Pediatrics

VOLUME 5 FEBRUARY 1950 NUMBER 2

ORIGINAL ARTICLES

KIDNEY FUNCTION IN YOUNG INFANTS

By HENRY L. BARNETT, M.D.
New York City

IT IS with gratitude that I accept this second E. Mead Johnson Award, being fully aware of the honor it brings to all of us who have shared in the work. The progress of the work has been stimulated by the encouragement and guidance given previously by Dr. Alexis F. Hartmann in St. Louis and, more recently, by Dr. Samuel Z. Levine in New York. I also wish to thank the doctors, nurses, technicians, secretaries and laboratory helpers who have actively participated and especially Miss Helen McNamara who makes the editorial "we" a reality. The nature of our studies required substantial financial support and we wish to express appreciation to the U. S. Public Health Service and the New York Heart Association for supplementing the excellent facilities for research at the New York Hospital-Cornell Medical Center.

It is the purpose of this paper to consider the development and present status of our knowledge of kidney function in young infants and to indicate some of its application to clinical problems. This knowledge is understandably incomplete because it is only during the last 10 years that the precise technics of kidney physiologists have been applied to the study of kidney function in young infants. The primary role of the kidneys in regulating the composition and volume of body fluids had been established earlier by an important series of observations, utilizing the technics of water and electrolyte balances. In many of these earlier observations there were already indications of an underdeveloped kidney function in young infants. Marples and Lippard,[1] for example, suggested that the high chloride content of serum in newborn infants was attributable to decreased ability to excrete chloride. It was not until 1940, however, after precise technics for estimating

E. Mead Johnson Award Address, read at the Annual Meeting, American Academy of Pediatrics, San Francisco, Calif., Nov. 17, 1949.

From the New York Hospital and the Department of Pediatrics, Cornell University Medical College, New York, N.Y.

Supported in part by research grants from the Divisions of Research Grants and Fellowships of the National Institutes of Health, U.S. Public Health Service and from the New York Heart Association, Inc.

(Received for publication Nov. 15, 1949.)

discrete kidney functions had been developed, that investigators undertook to study specifically the status of kidney function during early postnatal life. Gordon, Levine and others[2] at Cornell had noted that edema developed in some premature infants when they were changed from diets of human to cow's milk containing equivalent amounts of protein, fat, carbohydrate and fluid. This weight gain was accompanied by a lag in renal excretion of the extra sodium and chloride ingested in the cow's milk. These observations suggested the possibility of reduced kidney function in premature infants which Gordon, Harrison and McNamara[3] then investigated by the 24 hour urea clearance technic. Con-

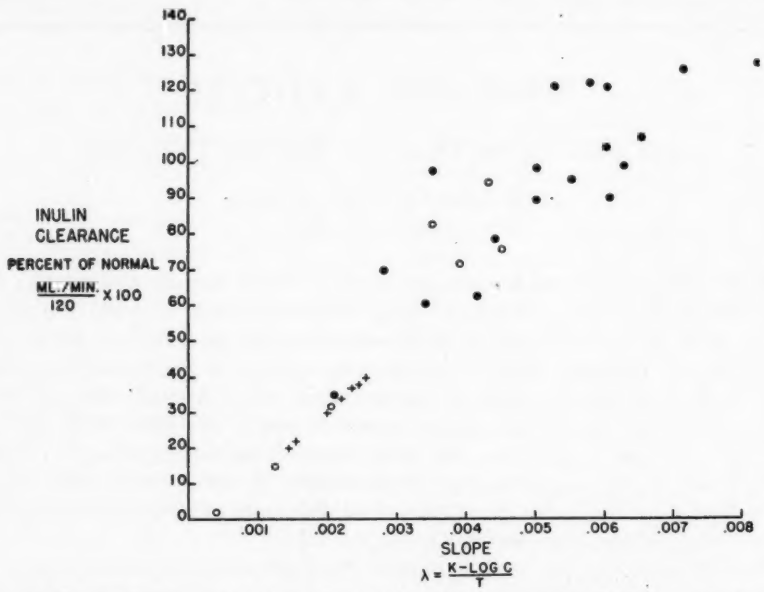

FIG. 1. Relation of inulin clearances to slopes of lines representing fall in plasma inulin concentration after intravenous injection. Dots represent data on children from 5 to 15 yrs. Circles represent points calculated from data of Alving and Miller. For explanation of crosses, see text.

currently, the interest of McCance, Young and others at the University of Cambridge had been aroused by the difficulty in obtaining satisfactory excretory pyelograms with diodrast in young infants. From this they suspected that newborn infants might have decreased diodrast clearances and they, too, investigated kidney function in these subjects employing at first urea clearances.[4,5] At Washington University in St. Louis, during this same period, our attention also had been directed to this subject by the report of Gruenwald and Popper[6] on the histology of the renal glomerulus in early postnatal life which suggested the possibility of a mechanical obstruction to glomerular filtration. Faced with the difficulty of obtaining quantitative urine collections in infants and children, we were attempting to correlate inulin clearances with the slope of the line representing the disappearance of inulin from the blood following a single intravenous injection of inulin.[7,8] The slope of such a line could provide a method for estimating glomerular

filtration rate which might obviate the necessity for urine collections. Values for the slope of this line determined in seven full term newborn infants and in older subjects plotted against measured inulin clearances in the older subjects are shown in Figure 1. Values for the infants depicted as crosses are seen to correspond to inulin clearances ranging approximately from 25 to 50% of the adult figure when corrected for surface area. These studies demonstrated that kidney function in early postnatal life is not fully developed.

I should like to turn now to a discussion of our present knowledge and to consider first the most important single specific measurement of kidney function, the measurement of glomerular filtration rate. The clearance of inulin is now well established as a measure of this function in adults. However, inulin and other substances commonly used in adult studies might conceivably be handled differently either by the immature kidney as such or by the immature organism as a whole. It was essential, therefore, to determine whether inulin clearances measured glomerular filtration rate in young infants. The clearance of any material excreted solely by glomerular filtration should be (1) independent of plasma concentration; (2) independent of rate of urine flow; (3) not influenced by the excretion of other substances, and (4) identical with that of other compounds known to measure glomerular filtration. We[9] have shown recently that the clearance of inulin in young premature infants satisfies these criteria: it is independent of plasma concentrations ranging from 12 to 68 mg./100 ml.; it is independent of rates of urine flow from .032 to 1.13 ml./min.; it is not influenced by glucose, mannitol or para-aminohippurate; it is identical with thiosulfate clearances and has the same ratio to mannitol clearances as it has in the adult. Inulin is, therefore, probably excreted solely by the glomerulus in young infants and we can accept its clearance as a measure of glomerular filtration rate. In all of the reported studies, including those of Dean and McCance,[10] of West, Smith and Chasis,[11] of Rubin, Bruck and Rapoport[12] and our own,[9] glomerular-filtration rate in newborn infants[9] has been found far below the adult value when corrected on the basis of surface area. This relative reduction is greater in premature infants in whom we have found inulin clearances ranging from 3 to 5 ml./min. The degree of reduction is only slightly less striking in full term newborn infants whose clearances range from 5 to 7 ml./min. Per unit of surface area* these values for premature and full term newborn infants represent approximately 33 and 40% of the adult value of 124 ml./min.

These findings immediately raised the intriguing question: what type of renal abnormality was responsible for the reduced rate of glomerular filtration in young infants? An impedence to filtration could be visualized from the histologic characteristics of the renal glomeruli shown in Figure 2.[13] Here the high columnar and cuboidal epithelium covering the visceral layer of Bowman's membrane and the unexpanded capillary tuft in the kidney of a premature infant are distinctly visible. Clearly the next step was to determine the proportion of plasma filtered at the glomerulus. It would be anticipated that this proportion, termed the filtration fraction, would be lower than in the adult if mechanical obstruction to filtration is responsible. This determination required the measurement of effective renal plasma flow.

* The relation of the clearances in young infants to surface area, body weight, kidney weight, metabolic rate, age or other standards of reference has not been fully established. This matter has been discussed by McCance,[4] West[11] and Rubin,[12] and for the present, at least, the surface area correction provides the best method for comparison with older subjects.

By virtue of the fact that at low plasma levels para-aminohippurate is almost completely removed from the blood in one passage through the kidneys, its clearance has been established by Smith[14] and others as a measure of effective renal plasma flow in adults. Simultaneous inulin and para-aminohippurate clearances in adults have revealed filtration fractions of 0.20 indicating that approximately one fifth of the 700 ml. of plasma flowing through the kidneys each minute is filtered by the glomeruli. Measurements of para-aminohippurate (or diodrast) clearances in premature or full term newborn infants have now been reported from the laboratories of McCance, Smith, Rubin and our own.

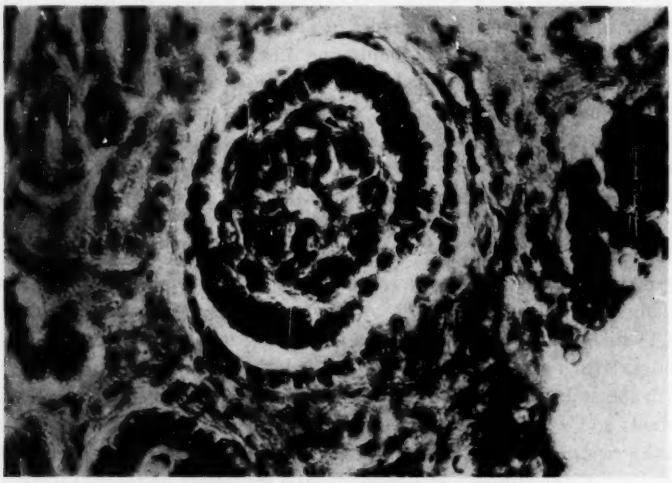

FIG. 2. Photomicrograph of glomerulus of premature infant.

We found an average value of 14.6 ml./min. in 13 premature infants ranging in age from 3 to 28 days.[9] Corrected for surface area this value is only 21% of the average value for adults. Only slightly higher values have been reported for full term newborn infants. In all of the reported studies the degree of reduction in para-aminohippurate clearances in young infants is greater than that of inulin clearances. Hence, contrary to expectation, the filtration fraction in young infants is actually higher than in adults. In our series of premature infants the average value was 0.34. This value indicates that one third of the minute renal plasma flow was filtered by the glomeruli in comparison with one fifth in adults. Though still above the adult value, Rubin found this fraction to be somewhat less than 0.34 in full term newborn infants. These findings, then, would indicate that the relatively reduced rate of glomerular filtration in young infants is not due to an impedence to filtration as the histologic appearance of the glomeruli suggest. The observations must, however, be interpreted with caution because acceptance of para-aminohippurate clearances as a measure of renal plasma flow depends upon para-aminohippurate being almost completely removed from the blood in one passage through the kidney, and this has not yet been demonstrated in young infants. Indirect evidence for and against the acceptance of these clearances as measures of renal plasma flow in young infants have been discussed by McCance[10] and by West,[11] but the final answer must await direct observations of extraction ratios.

The rate of postnatal development of these kidney functions provided the next logical step in these investigations. In their early studies, Gordon, Harrison and McNamara[3] had shown a striking rise in the 24 hour urea clearances of individual premature infants between the second and eighth week of life. More complete data are now available. The rate of maturation of glomerular filtration rate, which we consider to be the best established measurement in young infants, is shown in Figure 3 prepared from data of West[11] and of Rubin.[12] West's findings indicate that the adult mean value corrected for surface area may be reached in some infants as early as 10 to 20 weeks.

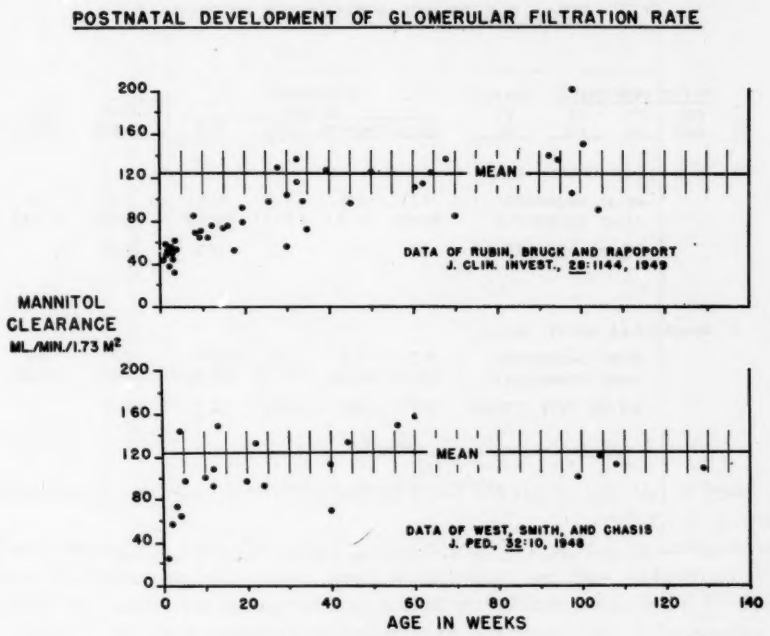

FIG. 3.

Rubin's data, on the other hand, show that in infants under 6 months of age, none of the values was within the adult range. They found many values in the adult range during the second year, but not all until the third year. We have isolated observations which agree with West that complete development may occur as early as 20 weeks of age. However, Rubin's data suggest that a broad range of 3 to 24 or more months must be accepted for the time at which infants achieve adult values on the basis of surface area.

The occurrence of premature births offers a unique opportunity to observe another aspect of maturation of kidney function.[15] Figure 4 shows values for various functions in two groups of premature infants of the same weight but of widely separated postnatal ages. These observations provide a possible basis for evaluation of the effect of function on maturational growth of the kidney. Even with the accepted limitations of body weight as an index of maturity, the great differences between birth weights of the two groups indicate an undeniable difference in their gestational ages at the time of birth.

Although there is evidence for limited prenatal kidney function, it can be inferred that during approximately the same period of gestational growth from 1,000 to 2,000 gm., the kidneys of the older infants were actively functioning to meet the responsibilities of extrauterine existence while those of the younger infants were relatively quiescent in their less demanding intrauterine environment. The mean values for the older group are significantly higher suggesting that greater function had accelerated the rate of maturation. The overlapping of the ranges, however, and the relatively small differences of the means suggest that the rate of postnatal development was not as rapid as might have been

RENAL CLEARANCES IN PREMATURE INFANTS

NO.	DAY OF OBSERVATION: AGE DAYS	WT. KG.	HT. CM.	BIRTH WT. KG.	CLEARANCES ML./MIN.: INULIN	MANNITOL	UREA	PAH	T_m PAH MG./MIN.	$\frac{C_{IN}}{C_{PAH}}$
8	3-13	2.1-2.4	46-47.5	2.1-2.5						
	MEAN: UNCORRECTED				4.7	4.2	2.9	14.6	1.3	.34
	RANGE: UNCORRECTED				3.3-6.6	3.1-6.1	1.8-4.1	9.9-16.5	0.6-2.3	.27-.42
	MEAN: PER 1.73 M^2				48	43	30	149	12.9	
9	49-107	2.2-2.5	43.5-47	0.7-1.4						
	MEAN: UNCORRECTED				6.9	5.8	4.5	20.6	2.2	.34
	RANGE: UNCORRECTED				5.1-11.1	5.1-6.8	2.7-8.0	12.8-35.0	1.2-5.3	.29-.42
	MEAN: PER 1.73 M^2				67	58	44	201	20.8	

FIG. 4.

anticipated in full term infants and that a limiting gestational factor may be operating in infants up to 2,500 gm.

Investigation of tubular function, including particularly renal mechanisms involved in the excretion of water and electrolytes in young infants are being actively pursued at present in many clinics. Smith,[16] in Boston, is investigating the role of the kidney in the adjustment of electrolytes and water following premature birth and Gordon[17] has studied the response of young infants to ingestion of ammonium chloride. Dean and McCance[18] have recently described the renal responses of infants to the administration of hypertonic solutions of sodium chloride and urea. A review of these and related studies is beyond the scope of this paper, but one important requirement for such studies should be stressed. This requirement, which has not yet been fully satisfied, is for a technic of measuring glomerular filtration rate over extended periods of time, since this measurement serves as the reference point for interpreting the role of tubular transport of other substances. Such a technic demands the use of an endogenous substance whose clearance equals or bears a constant relation to inulin clearances. The clearance of urea does not satisfy these requirements. Goldstein,[19] working in our clinic, has shown that urea clearances in premature infants are not affected by wide variations in protein intake. On the other hand we have shown that urea clearances are dependent upon several other independent variables, including glomerular filtration, tubular transfer of water and rate of change of urine flow.[9] The changing relationship between inulin and urea clearances with changes in urine flow in premature infants is shown in Figure 5.

It can be seen that urea clearances do not bear a constant relationship to inulin clearances and, therefore, cannot be used as a measure of glomerular filtration rate. Endogenous creatinine clearances, on the other hand, may provide the essential technics. Using the method of Hare and Hare[20] for the determination of serum creatinine, we have found with Hare, Goldstein and Hare[21] that endogenous creatinine clearances are equal to simultaneously determined inulin clearances in young infants. Although this finding is not established completely as yet, endogenous creatinine clearances may provide the medium for measuring glomerular filtration rate over extended periods of time.

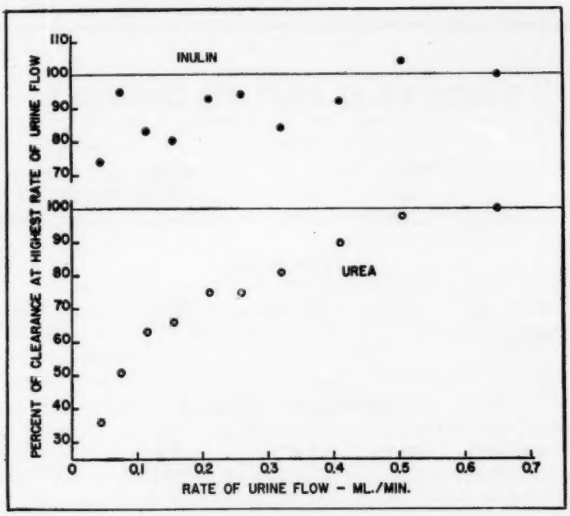

FIG. 5. Changes in inulin and urea clearances with changes in rate of urine flow in premature infants. These data were calculated from 100 simultaneous inulin and urea clearances. Each point represents average of 10 periods. Clearances are expressed as per cent of average clearance at highest average rate of urine flow observed.

This newer knowledge of kidney function in young infants, though incomplete, is finding increasing application to clinical problems. Before discussing some of these it should be pointed out that under most circumstances the kidneys of even the youngest premature infants do a remarkably creditable job. Yet even under conditions considered optimal, there are indications of immaturity of kidney function during early postnatal life. The moderately increased concentration of serum chloride and potassium and the lowered bicarbonate concentrations in premature infants receiving cow's milk are probably indications of immature kidney function. These chemical differences from full term or older premature infants produce no apparent disturbance and their clinical significance, therefore, can be questioned. However, only slight deviations from optimal conditions, which are handled by the more mature kidneys of older infants, may produce profound symptoms in young premature infants. The production of acidosis in premature infants by protein milk, described by Darrow[22] and his associates and recently

confirmed by Hoffman[23] and others, is a striking example of the handicap imposed by the limitation of kidney function. This same limitation provides a physiologic basis for using hypotonic solutions of sodium chloride for repair of dehydration in young infants, the value of which is becoming increasingly apparent. Quite a different type of limitation of the incompletely developed kidney may play a role in tetany of the newborn, as suggested by Snelling. McCrory and Forman,[24] in our laboratory, are at present studying the renal mechanisms which may be involved in this poorly understood disease.

One final general clinical application of these findings deserves emphasis. Establishing proper dosage of drugs for very young infants should include consideration of their

CLEARANCES OF INULIN AND PENICILLIN G

NO.	AGE	WT. KG.	HT. CM.	MEAN CLEARANCES ML. PER MIN. PER 1.73 M^2 INULIN	PENICILLIN G
			CHILDREN		
12	3-12 YRS.	13-46	95-150	127 (93-145)	560 (311-954)
			PREMATURE INFANTS		
4	4-8 DAYS	2.2-2.3	47-47.5	44 (31-53)	90 (72-114)

FIG. 6.

reduced kidney function, if renal excretion of the drug occurs. Figure 6 shows a comparison between penicillin clearances in premature infants and in children,[25] and serves to illustrate this principle. Corrected for surface area the mean clearance value for penicillin in premature infants is 90 compared with 560 ml./min./1.73 sq. m. in the children. This degree of reduction in penicillin clearances suggests that if penicillin is given to premature infants in dosages proportionate to their surface area and if the rate of absorption is the same, the duration of drug concentrations in the blood should be six times as long as in children and adults. If given in dosages proportionate to their weight, the more common practice, levels should be maintained three times as long. Similar evaluation of the effect of reduced renal clearances on dosage of other drugs used in young infants is clearly indicated.

Assembling and presenting this material has been gratifying and at the same time challenging. It has been gratifying because our present knowledge of this subject reflects so clearly the value of approaching a problem with the co-ordinated efforts of the physiologist and the clinical investigator. It is challenging because the extension of basic

knowledge must include its application to clinical problems by the indispensable third member of the team, the clinician.

References

1. Marples, E., and Lippard, V. W., Acid-base balance of newborn infants. II. Consideration of low alkaline reserve of normal newborn infants, Am. J. Dis. Child. **44**:31, 1932.
2. Gordon, H. H., Levine, S. Z., Wheatley, M. A., and Marples, E., Respiratory metabolism in infancy and in childhood. XX. Nitrogen metabolism in premature infants: Comparative studies of human milk and cow's milk, Am. J. Dis. Child. **54**:1030, 1937.
3. Gordon, H. H., Harrison, H. E., and McNamara, Helen, Urea clearance of young premature and full term infants, J. Clin. Investigation **21**:499, 1942.
4. McCance, R. A., and Young, W. F., Secretion of urine by newborn infants, J. Physiol. **99**:265, 1941.
5. Young, W. F., Hallum, J. L., and McCance, R. A., Secretion of urine by newborn infants, Arch. Dis. Child. **16**:243, 1941.
6. Gruenwald, P., and Popper, H., Histogenesis and physiology of renal glomerulus in early postnatal life: Histological examinations, J. Urol. **43**:452, 1940.
7. Barnett, H. L., Renal physiology in infants and children. I. Method for estimation of glomerular filtration rate, Proc. Soc. Exper. Biol. & Med. **44**:654, 1940.
8. Barnett, H. L., Perley, A. M., and McGinnis, H. G., Renal physiology in infants and children. II. Inulin clearances in newborn infant with extrophy of bladder, Proc. Soc. Exper. Biol. & Med. **49**:90, 1942.
9. Barnett, H. L., Hare, K., McNamara, Helen, and Hare, R., Measurement of glomerular filtration rate in premature infants, J. Clin. Investigation **27**:691, 1948.
10. Dean, R. F. A., and McCance, R. A., Inulin, diodone, creatinine and urea clearances in newborn infants, J. Physiol. **106**:431, 1947.
11. West, J. R., Smith, H. W., and Chasis, H., Glomerular filtration rate, effective renal blood flow, and maximal tubular excretory capacity in infancy, J. Pediat. **32**:10, 1948.
12. Rubin, M. I., Bruck, E., and Rapoport, M., Maturation of renal function in childhood, J. Clin. Investigation **28**:1144, 1949.
13. Hare, K., Ungewitter, L., Barnett, H. L., and McNamara, Helen, Observations on structure and function of glomerulus in premature and full term infants, Fed. Proc. **7**:51, 1948.
14. Smith, H. W., Finkelstein, L. A., Crawford, B., and Graber, M., Renal clearances of substituted hippuric acid derivatives and other aromatic acids in dog and man, J. Clin. Investigation **24**:388, 1945.
15. Barnett, H. L., Hare, W. K., McNamara, Helen, and Hare, R. S., Influence of postnatal age on kidney function of premature infants, Proc. Soc. Exper. Biol. & Med. **69**:55, 1948.
16. Smith, C. A., and others, Adjustment of electrolytes and water following premature birth (with special reference to edema), PEDIATRICS **3**:34, 1949.
17. Gordon, H. H., McNamara, Helen, and Benjamin, H. R., Response of young infants to ingestion of ammonium chloride, PEDIATRICS **2**:290, 1948.
18. Dean, R. F. A., and McCance, R. A., Renal responses of infants and adults to administration of hypertonic solutions of sodium chloride and urea, J. Physiol. **109**:81, 1949.
19. Goldstein, H., Effect of protein intake on blood urea nitrogen and kidney function in premature infants, to be published.
20. Hare, R. S., and Hare, K., Determination of creatinine in blood and urine, Fed. Proc. **8**:68, 1949.
21. Hare, K., and others, Renal excretion of creatinine in man, Fed. Proc. **8**:67, 1949.
22. Darrow, D. C., da Silva, M. M., and Stevenson, S. S., Production of acidosis in premature infants by protein milk, J. Pediat. **27**:43, 1945.
23. Hoffman, W. S., Parmelee, A. H., and Grossman, A., Mechanism of production of acidosis in premature infants by protein milk, Am. J. Dis. Child. **75**:637, 1948.
24. McCrory, W., and Forman, C., Personal communication to the author.
25. Barnett, H. L., McNamara, Helen, Shultz, S., and Tompsett, R., Renal clearances of sodium penicillin G, procaine penicillin G, and inulin in infants and children, PEDIATRICS **3**:418, 1949.

525 East 68th Street

"GREEN STOOL SYNDROME" OF THE NEWLY BORN INFANT

By I. J. GREENBLATT, PH.D., HARRY BLOCH, M.D., R. D. TURIN, M.D., AND S. DAVID STERNBERG, M.D.
Brooklyn, N.Y.

THIS report concerns the occurrence in epidemic proportions of green, bile-stained stools in 81 newborn infants over a three week period. In the beginning, it was believed to be the start of an epidemic of toxic diarrhea of newborn infants. Toxic symptoms did not develop at any time during the course of observation.

Epidemic diarrhea of the newborn infant has been the subject of a great deal of clinical and laboratory investigation with only a limited degree of success. Mayes,[1] in a report of an outbreak, attributed the diarrhea to a failure of the infants to develop a normal intestinal flora. He even suggested as therapy the inoculation of feces from a normal infant into the rectum of an ill patient, to establish a normal flora. Olivier and his co-workers[2] attributed an outbreak of diarrhea in infants to some alteration or inadequacy of the intestinal flora. Most of their patients were afebrile. As a therapeutic measure, they fed the infants a viable culture of B. subtilis 3 mg. in six divided doses in 24 hours. Within a 48 hour period, the stools were normal and the patients became asymptomatic. Unfortunately, the bacteriologic examinations of the feces were incomplete in their report.

CLINICAL OBSERVATIONS

In a period of 3 wks., 81 newborn infants were observed with green, bile-stained stools. They were all asymptomatic, afebrile and took nourishment normally and continued to gain weight. There was no frequency of bowel movements. The youngest group was made up of 3-day old infants, of which 31 were seen. Of the 4-day old group, 24 cases were observed. Twenty cases were seen in the 5-day old group and 6 cases in the 6-day old group. There were 47 males and 34 females. In no instance did these patients meet the criteria of diarrhea of the newborn infant as defined by the California State Department of Health.[3] The incubation period was 3 days. Only 4 cases showed a mucoid acellular stool.

The epidemiologic characteristics of this outbreak were established by the use of suspect and isolation nurseries. Clinical and bacteriologic examinations of the personnel and detailed review of the formula room technic and equipment were negative. No chemical agent, cleansing material or foreign pigment was uncovered from the food (a mixture of dextrimaltose, water and evaporated milk), food containers and paraphernalia used in preparing the infant's food.

LABORATORY STUDIES

A. Bacteriology of Stools. Nearly all the stool specimens were of normal consistency, green, free of cellular elements, with a marked paucity of organisms on direct smear. Bacteriologic examinations were negative for pathogens. Twelve of the stool specimens showed "no growth" even on enriched media. Of 91 specimens examined, 2 showed a coagulase-positive Staph. aureus. No fungi were recovered.

B. Biochemical Studies. The green stools suggested that urobilinogen would be absent in the urine. Urine and fecal specimens from 16 infants exhibiting the green stools were obtained and examined for urobilinogen and bile. Table I summarizes the results of the tests.

An alteration in prothrombin time might be expected because the bacterial synthesis of vitamin K would not proceed at a normal rate. Schmidt and Busig[4] as well as Welch and Wright[5] have stressed this fact.

From the Biochemical Laboratory and the Department of Pediatrics, Beth-El Hospital, Brooklyn, N.Y.

(Received for publication May 10, 1949.)

TABLE I

FECAL AND URINE BILE AND UROBILINOGEN IN 16 INFANTS

No.	Age	Fecal Urobilinogen	Urine Urobilinogen	Fecal Bile	Urine Bile
6	3 days	−	−	+	−
7	4 "	−	−	+	−
2	5 "	−	−	+	−
1	6 "	−	−	+	−

Prothrombin determinations were done on 13 of the 16 infants' blood plasmas using Quick's 2 step technic.[6] Six normal infants who had not had the green stool syndrome were used as controls. The striking differences in both groups can be seen in Table II.

In 7 cases, follow-up blood studies were obtained on the patients with low prothrombin levels following the injection of penicillin. The prothrombin levels were normal within 48 hrs. following the administration of penicillin. At this time, the urine and feces were positive for urobilinogen. The blood zinc turbidity test, the cephalin flocculation test and the icterus indices in the 16 ill infants tested were within normal limits. No hematologic disorders were noted.

In a control group of 6 patients with the green stool syndrome, none cleared spontaneously after 11 days of observation. Their stools subsequently became normal within 24 hrs. following penicillin therapy.

Penicillin was administered parenterally on a purely empiric basis with good effects. Within 24

TABLE II

COMPARISON OF PROTHROMBIN ACTIVITY OF 13 PATIENTS WITH "GREEN STOOL SYNDROME" WITH THOSE OF 6 NORMAL CONTROLS

Patients			Controls		
No.	Age	Average Prothrombin Activity	No.	Age	Average Prothrombin Activity
4	3 days	37%	2	3	81%
6	4 days	43%	2	4	110%
2	5 days	42%	2	5	102%
1	6 days	31%	X	X	X

15.8 sec.—100%.

hrs., the stools reverted to normal. The infants not receiving penicillin continued to exhibit the green stool syndrome. After one injection of 100,000 units of aqueous procaine penicillin, the urine and feces became urobilinogen positive within a period of 24 hrs. A faint trace of fecal bile was occasionally found by chemical means. This was apparently due to bile which had not been completely converted to urobilinogen. The bile was negative and urobilinogen positive in the feces of the normal controls.

DISCUSSION

Following the use of penicillin and the response shown by the patient, the possibility was entertained of an organism secreting an antibiotic which was causing a depression of growth of the abnormal flora of the bowel. Apparently the syndrome was caused by a penicillin-sensitive agent which did not interfere with the nutrition of the infants but which depressed the normal intestinal flora. The possibility of a phage was discarded

for many reasons, particularly in view of the therapeutic effect of penicillin. After a single dose of 100,000 units of aqueous procaine penicillin parenterally, the gross and bacteriologic fecal findings reverted to the normal state. Greenblatt and Greenblatt[7] showed that urobilinogen production can be markedly decreased in humans by oral administration of sulfaguanidine. This drug depressed bacterial activity in the gastrointestinal tract.

The concept of the conversion of bilirubin to the colorless mesobilirubinogen and then final reduction to urobilinogen in the intestinal tract by bacterial organisms, as postulated by Watson,[8] is widely accepted. This process begins within a few hours after birth and the human host lives with the intestinal flora in a symbiotic relationship. Snyder[9] showed that within two hours after birth as many as 15 different strains of organisms could be isolated from the intestinal tract of the newborn infant.

The most disturbing element in the evaluation of results is the inability to demonstrate a specific organism exhibiting antibiotic properties. Although the green stools were mixed with normal stools, results were too equivocal to claim the existence of a specific antibiotic in the former. However, the almost complete absence of organisms in many specimens and the failure to obtain growth in many specimens substantiated the belief that a factor which depressed the growth of the normal intestinal flora in the newborn infant was present. Virus studies were not done. The high sensitivity of the unknown factor to penicillin suggests that a microscopically visible body, probably bacterial in nature, rather than a phage or virus, is the etiologic agent in "green stool syndrome."

Epidemiologically, this syndrome is highly contagious. Investigation of all the steps involved from the moment of birth to the first feeding was carefully screened, rechecked and found to be epidemiologically sound. As many as nine new cases a day occurred followed by a secure period for a few days, with new cases reappearing, despite all efforts at control by isolation and dietary technics. It is important not to label a green stool as epidemic diarrhea of the newborn infant unless accompanied by the toxic symptoms.

Conclusions

A syndrome in newborn infants consisting of green stools, normal number of bowel movements, without pyrexia, dehydration, vomiting or death, is described.

No etiologic agent was uncovered but metabolic changes as evidenced by low prothrombin and absence of urobilinogen in the feces and urine were seen.

The appearance of normal bacteriologic flora of the feces as evidenced by culture, smear and the presence of urobilinogen, and normal prothrombin activity following treatment suggest that a penicillin-sensitive agent which exerted antibiotic effects on the normal intestinal flora was present.

Acknowledgment

The authors wish to express appreciation to Miss G. Rabinowitz and Miss D. Ward for their cooperation in this work.

References

1. Mayes, H. W., Epidemic diarrhea in newborn: Relation between breast and bottle feeding and early development of intestinal flora, Am. J. Obst. & Gynec. **53**:285, 1947.
2. Olivier, H. R., Blanchon, E., Saint-Rat, L., and Bonet-Maury, P., Utilisation du bacille subtilis dans le traitement des diarrhées, Arch. d. mal. de l'app. digestif. **34**:183, 1945.
3. California State Dept. of Health Bulletin, May 15, 1943, vol. 22, no. 17.

4. Schmidt, T., and Busig, K. H., Interrelationship between vitamin K and intestinal bacterial flora, Klin. Wchnschr. **21**:411, 1942.
5. Welch, A. D., and Wright, L. D., Role of "folic acid" and biotin in nutrition of rat, J. Nutrition **25**:555, 1943.
6. Quick, A. J., Clinical application of hippuric acid and prothrombin tests, Am. J. Clin. Path. **10**:223, 1940.
7. Greenblatt, I. J., and Greenblatt, A. P., Effects of sulfaguanidine on urobilinogen and urobilin metabolism, Arch. Biochem. **7**:87, 1945.
8. Watson, C. J. A., Studies of urobilinogen: Per diem excretion of urobilinogen in common forms of jaundice and disease of liver, Arch. Int. Med. **59**:205, 1937.
9. Snyder, M. L., Bacterial flora of meconium specimens collected from 64 infants within four hours after delivery, J. Pediat. **9**:633, 1936.

SPANISH ABSTRACT

"Síndroma de Deposición Verde" en el Infante Recién-Nacido

Se describe un síndroma en infantes recién-nacidos consistiendo en deposiciones verdes, número normal de movimientos intestinales, sin pirexia, deshidratación, ni vómitos ni muerte.

No se descrubrió ningún agente etiológico, per si se vieron cambios metabólicos somo la baja protrombina y la ausencia de urobilina en los excrementos y en la orina.

La apariencia de la flora bacteriológica normal de los excrementos observada por el cultivo, frotis y la presencia de urobilinogeno y la actividad de protrombina normal después del tratamiento sugiere que un agente sensible a la penicilina con efectos antibióticos en la flora normal intestinal estaba presente.

Rockaway Parkway and Avenue A

ANALYSIS OF FETAL AND NEONATAL DEATHS IN 4117 CONSECUTIVE BIRTHS

By HERBERT C. MILLER, M.D.
Kansas City, Kan.

THE causes of neonatal death are in many cases considered to be obscure and are often couched in vague terms, such as "prematurity," "immaturity," "anoxia" or "anoxic injuries." Most of the vague terminology applies particularly to the mortality of premature infants, which accounts for approximately half of all neonatal deaths. The prevalent opinion on this subject has been summarized recently by Dunham[1] in her book *Premature Infants,* in which she states, "Determining the exact cause of death of a premature infant is often difficult. Postmortem examination will often throw light on the cause of death; but, even if clinical and postmortem examinations are made carefully, there will still be a large proportion of cases in which no specific cause of death is determined, because many very immature infants, born alive, die simply because development has not advanced to the point at which extra-uterine existence is possible." Data are shown in her book pointing out that prematurity alone (no abnormalities) was the chief cause of death found in 121 autopsies out of 348 done on premature infants weighing between 1000 and 2500 gm. at birth by Potter at the Chicago Lying-In Hospital. Recent studies from other hospitals report similar findings.[2-4] This lack of significant pathologic findings and the fact that premature infant fatality rates vary inversely with the birth weight have led to the concept that the premature infant's chances for survival will be increased largely by overcoming specific deficiencies or by preventing their occurrence by prolonging fetal existence.

Recent studies of the lungs of newborn infants dying in the first few days of life in the nurseries of the University of Kansas Medical Center have revealed that a large proportion of premature infants died with large amounts of hyaline-like material in their lungs.[5,6] It was concluded from these investigations that the pulmonary lesions were not the result of aspirated amniotic sac contents, as previously thought, but were the result of some injury to the epithelium and walls of the terminal air spaces by some unknown agent. Because of the high incidence of these lesions in the lungs of premature infants and the new interpretation put upon them, an attempt has been made in the present report to analyze the possible role of these pulmonary lesions in causing neonatal death in comparison with other significant pathologic conditions. Since the study on which the data in the present investigation were based included all fetal as well as neonatal deaths in a series of 4117 consecutive births in this hospital from 1944 to 1948 inclusively, the analysis of the causes of death was extended to include all fetuses dying before birth as well as all infants who died in the neonatal period.

The results of the analysis of the causes of neonatal death in this group of infants were in agreement with those recently reported by Arey,[7] who found adequate causes of death in 43 of 50 live-born infants. It is the purpose of this report to indicate that most

From the Department of Pediatrics, University of Kansas School of Medicine, Kansas City, Kan.
(Received for publication March 16, 1949.)

of the neonatal deaths in the present study were associated with specific pathologic conditions and that further significant reductions in neonatal mortality are not to be expected until the pathogenesis of these conditions and their satisfactory treatment have been discovered.

Material

The material in the present study was the same as that used in the preceding report.[6] The causes of neonatal death in the autopsied infants of the present study were taken from Tables VI and VII of that report. It was observed in a considerable number of autopsied infants that more than one pathologic condition of a serious nature was present. For instance, in Case 18 of Table VII there were present sclerema, a polycystic kidney and cerebral atrophy. The decision as to which of these conditions was the primary cause of death seemed to be a highly arbitrary one and the same could be said for the other infants in whom more than one serious pathologic condition was found. Hence, no attempt has been made to specify which condition was the primary cause of death. The tables in this report have been prepared to show the various types of serious pathologic conditions which were probably significant factors in causing death and to show the number of infants who died with such significant findings. If two significant causes of death were found, both were included in the tabulated data, but the infant was counted only once.

Results

Causes of neonatal death: The number of live births, neonatal deaths, autopsies, infants dying with significant causes and the types and incidences of the various significant causes of death are shown in Table I.

Infants weighing less than 1,000 gm. at birth were included in the data in Table I to indicate that they formed a special group. There were 20 live births in this weight group and 17 deaths, giving a fatality rate of 85%, which, as Dunham[3] has shown, is in accord with rates being reported from other centers. Autopsies were done on 14 of the 17 infants who died and there were only 4 instances in which a significant cause of death could be found. The inability to find a significant cause of death in 10 of the 14 infants in spite of autopsies having been done is in keeping with studies made in other clinics on infants of similar birth weight. It seems likely that the nondescript term "immaturity" can well be applied to describe the cause of death of most of these infants in the present state of our ignorance as to specific causes.

There were 355 live-born infants who weighed between 1000 and 2500 gm. at birth with 40 neonatal deaths or a fatality rate of 11.2%. Autopsies were done on 33 infants. In 29 of these infants, 42 significant causes of death were found. The most frequent significant cause of death in this group of 29 infants was the presence of hyaline-like material in the lungs, having been observed in 16 infants. It is not known how extensive this lesion must be to cause death. An arbitrary amount was set in the present study based on the investigation reported in the preceding paper.[6] In the latter report the amount of hyaline-like material in the lung was graded on a scale of 1 to 4 from studies of microscopic sections of the lungs. If the hyaline-like material received a rating of 3 or 4, it was considered to be a significant cause of death in the present report. There were 6 infants in the birth-weight group under discussion who were found at autopsy to have extensive cerebral hemorrhages. Four infants had serious congenital malformations, including coarctation of the aorta, polycystic kidney and cerebral agenesis, porencephaly and hydrocephalus. If infants had multiple severe congenital malformations, only 1 of them was considered as a significant cause of death. Four infants had sclerema and 4 had pneumonia. Pneumonia was not diagnosed unless there were patchy areas throughout the lung showing heavy concentrations of polymorphonuclear leucocytes together with mononuclear cells in the lumen of the alveoli. Anoxia was considered as a significant cause of death in 3 infants, all of whom died 8 hrs. after births complicated by premature separation of the placentas. Syphilis, sepsis, hydrops fetalis, cirrhosis of the liver and maternal diabetes were considered as significant causes of death in 1 child each. Maternal diabetes was listed among the significant causes of neonatal death because of the high fetal and neonatal mortality associated with this disease, even though the exact manner in which death occurs in the fetus or live-born infant is not understood. To have included such infants under a nondescript term or as having died of some unknown cause would have served no useful purpose. There were 13 infants who had multiple significant causes of death; 12 had at least 2 and 1 infant had 3 significant causes. There

TABLE I

CAUSES OF DEATH AMONG 4051 CONSECUTIVELY LIVE-BORN INFANTS

B.W. kg.	Total Births	Neonatal Deaths and Rate	Total Autopsies	Infants Dying With Significant Causes			Infants Autopsied; no Significant Cause Found	Types and Incidence of Significant Causes	
				Total	Autopsied	Not Autopsied		Types	Incidence
less than 1	20	17 (85%)	14	4	4	0	10	syphilis	1
								cerebral hemorrhage	1
								sclerema	1
								anoxis (placenta previa)	1
								Total	4
1–2.5	355	40 (11.2%)	33	29	29	0	4	hyaline-like material	16
								cerebral hemorrhage	6
								congenital anomaly	4
								sclerema	4
								pneumonia	4
								anoxia (premature sep. pl.)	3
								syphilis	1
								sepsis	1
								hydrops fetalis	1
								cirrhosis of liver	1
								maternal diabetes	1
								Total	42
2.5 or more	3,676	28 (0.7%)	24	23	19	4	5	congenital anomaly	8
								anoxia	4
								dystocia-2	
								"suffocated" in crib-1	
								prolapsed cord-1	
								hyaline-like material	3
								kernicterus	3
								pneumonia	2
								cerebral hemorrhage	2
								maternal diabetes	2
								sepsis	1
								sclerema	1
								Total	26
Total	4,051	85	71	56	52	4	20		

were 4 infants in the group whose birth weights ranged from 1000 to 2500 gm. who were autopsied, but were considered to have insufficient evidence of a significant cause of death. Three of the 4 infants had hyaline-like material in their lungs in small amounts (grade 1); possibly with more extensive microscopic studies of the lungs more of this material might have been found. The 4th infant weighed 1040 gm. at birth, which is close to the weight group that has been shown in this and other studies to have a low incidence of significant specific autopsy findings. Seven infants in this group were not autopsied and no significant cause of death could be assigned to any of the 7.

There were 3676 live-born infants who weighed over 2500 gm. at birth and 28 died in the neonatal period, a fatality rate of 0.7%. Twenty-four autopsies were done. Twenty-three infants were observed for whom a significant cause of death could be found. Nineteen of the 23 infants had postmortem examinations. The 4 who were not autopsied had anencephaly, hydrocephalus, sclerema and maternal diabetes as significant causes of death. The most frequent significant cause of death in the group of 23 infants was congenital malformation, which occurred in 8 infants. Anoxia accounted for 4 other infants; 2 of the 4 were born after long labors; 1 died a few minutes after resuscitation following birth; a 3rd infant was "suffocated" in his crib; the 4th died at 7 hrs. of age, labor having been complicated by a prolapsed cord. Hyaline-like material was present in large

amounts in 3 infants and kernicterus was found in 3 infants. Pneumonia, cerebral hemorrhages and maternal diabetes occurred as significant causes of death in 2 infants each; sepsis and sclerema, in 1 infant each. Multiple significant causes of death were found in 2 infants. One of these had large amounts of hyaline-like material in the lung and pneumonia; the other had staphylococcus septicemia, pneumonia and kernicterus. Five infants were autopsied, but no significant cause of death was found: 2 of these infants had hyaline-like material in their lungs in small amounts (grade 1); 1 infant was born to a mother who had toxemia of pregnancy, which was not considered as a significant cause of death in any live-born infant in this study; in 1 infant the diagnosis of erythroblastosis fetalis was seriously considered but, because there was some doubt, the infant was put in the undiagnosed group; the 5th infant was born to a mother who had a 4+ blood Wassermann on admission with a questionable history of antiluetic therapy and the infant died on the 7th day, but it was not clear from the autopsy as to whether the infant had syphilis. These 5 infants were the only ones in this group for whom no significant cause of death was determined.

The percentage of cases in which a significant cause of death was found is high in this study if no consideration is given to infants who weighed 1000 gm. or less at birth. This is a special group as shown above. In the group of 68 infants who weighed 1000 gm. or more at birth there were 52 or 76% for whom a significant cause of death was demonstrable, as shown in Table I. If only

TABLE II

CAUSES OF 66 FETAL DEATHS* IN 4117 CONSECUTIVE BIRTHS

B.W. kg.	Total Died	Antepartum Deaths				Intrapartum deaths			
		Total	Autopsies	Died Significant Causes	Significant Causes	Total	Autopsies	Died Significant Causes	Significant Causes
1 or less	2	2	0	2	congenital anomaly. 1 tox. of preg..... 1	0	0	0	
1–2.5	28	14	2	9	anoxia..... 1 1 premature sep. pl. tox. of preg..... 5 maternal diabetes... 2 congenital anomaly. 1 "flu" in mother.... 1	14	11	13	anoxia..... 8 3 placenta previa 2 premature sep. pl. 2 prolapsed cord 1 dystocia cerebral hemorrhage. 3 tox. of preg..... 2 maternal diabetes.... 1 hydrops fetalis..... 1 maternal pneumonia. 1 Total.....16
2.5 or more	36	18	2	11	anoxia..... 5 1 {prem. sep. pl. / true knot cord} 1 thrombus of cord 1 hematoma of cord 1 prolapsed cord 1 infarcted placenta syphilis (maternal).. 3 tox. of preg..... 1 congenital anomaly. 1 maternal diabetes... 1 Rh sensitization.... 1	18	7	16	anoxia..... 8 4 dystocia 2 prolapsed cord 1 placenta previa 1 premature sep. pl. fetal pneumonia..... 3 tox. of preg..... 2 maternal diabetes.... 1 laceration of liver.... 1 cerebral hem..... 1 Total.....16
Total	66	34†	4	22		32	18	29	

* So far as could be judged from the obstetric records, no respiratory movements and no heart beats were observed following the birth of any of these fetuses.

† 17 of these fetuses had gross postmortem examinations but no microscopic studies.

autopsied infants are considered, it is seen from the data in Table I that 48 of the 57 autopsied infants or an incidence of 84% had significant causes of death. Among the 11 infants who were not autopsied there were only 4 with significant causes of death assigned to them. The incidence of infants who were autopsied and weighed between 1000 and 2500 gm. at birth and for whom no significant cause of death could be found was 4 out of a total of 33 or 12%. This incidence is considerably lower than that quoted by Dunham of 34% in a group of 348 premature infants in a similar weight group reported by Potter.[1]

Causes of fetal death: Causes of fetal death are given in Table II according to birth weight and according to whether death occurred antepartum or intrapartum. Although there were only 22 autopsies done which included gross and microscopic studies, it was possible to find a significant cause of death in 51 of the 66 fetuses, largely because there was so often some obvious and serious complication of pregnancy or labor. A diagnosis of a significant cause of death was made in practically the same proportion of cases among the fetuses in this study as among live-born infants in spite of the fact that the incidence of autopsies was almost a third less in the former group. Significant causes of fetal death were found about equally in the antepartum and intrapartum groups. There were 22 out of 34 fetuses in the former group and 29 out of 32 fetuses in the latter group for which significant causes of death could be determined.

The chief cause of fetal death was anoxia. Six antepartum and 16 intrapartum deaths were observed to have been associated with anoxia. Seventeen of the 22 anoxic deaths were related to accidental interruptions of the supply of oxygen to the fetus through the placenta and umbilical vessels; the other 5 deaths were associated with dystocia. Toxemia of pregnancy including eclampsia was the next most frequent significant cause of fetal death, having been present in 11 instances, 7 of them in the antepartum period. The toxemias of pregnancy were not considered as significant causes of neonatal death, because there is no evidence that the live-born infant dies as a result of the mother's toxemia. There is abundant evidence, however, that maternal toxemia carries a considerable risk for the fetus and consequently it is considered a significant cause of fetal death, although it is not understood by what mechanism death in utero occurs. Diabetes mellitus was the next most common significant cause of death; there were 5 such cases, 3 of them occurring in the antepartum period. Maternal infections accounted for 5 fetal deaths, including 3 cases of syphilis, 1 of pneumonia and 1 of "flu."

It is observed that among fetuses weighing over 1000 gm. maternal disease or complications of labor were significant causes of fetal death in 42 or 65% out of a total of 64 cases. This high incidence is in marked contrast to the relatively minor role that maternal complications of pregnancy or labor played in the production of neonatal death. There were 10 instances, 14%, out of a total of 68 infants who weighed over 1000 gm. at birth in which maternal disease or problems connected with labor could be considered as significant causes of neonatal death, as shown in Table I. These 10 cases included 6 in which anoxia was a significant cause, 3 of diabetes mellitus and 1 of syphilis. Diseases or defects in the fetus were considered as significant causes of fetal death in 14 cases: there were 4 fetuses that had congenital malformations, 4 that had cerebral hemorrhages, 3 with pneumonia, 2 in which Rh sensitization was a significant cause and 1 with a lacerated liver. A comparison of the causes of death of fetuses and live-born infants weighing over 1000 gm. at birth showed that 13 or 23% of the 55 significant causes of fetal death listed in Table II were diseases or defects of the fetus or infant, while 59 or 85% of the 68 causes in Table I could be so considered.

One of the striking facts associated with neonatal death in the present study was the different types of significant causes of death that were observed in premature as compared to full term infants. This difference did not pertain to fetal deaths. There was a considerable similarity in the causes of death among premature and full term fetuses, anoxia having been present in 9 of the 28 fetuses that weighed between 1000 and 2500 gm. and in 13 of the 36 that weighed over 2500 gm. There was a slight but not significant discrepancy between the 2 groups in the incidence of toxemias of pregnancy, the only other significant cause which occurred sufficiently often to be considered.

No significant cause of death was found for 15 fetuses, 12 of which were macerated. In the latter group were 7 fetuses the mothers of which were over 35 yrs. of age. Nine of the macerated fetuses were Negroes; 5 were premature by birth weight. Seven of the 12 macerated fetuses had gross autopsies done without significant findings. There were 3 fetal deaths in the antepartum group that remained unexplained; all 3 were Negroes; 2 of the 3 mothers were over 30 yrs. of age and 1 of the 2 mothers was over 35 yrs. old.

Discussion

The determination of the primary cause of death in newborn infants is often difficult. The factors involved in the birth process are difficult to assess; the duration of life in many infants is a matter of hours; the changes taking place following birth are many and important and the technics for determining pathologic alterations in physiology and anatomy in live newborn infants are poorly developed. To claim that a newborn infant died of a cerebral hemorrhage or pneumonia often involves an arbitrary decision even though the claim has been based on a complete autopsy. The decision becomes more difficult and arbitrary when two or more serious conditions are present, as is often the case in premature infants. It was for these reasons that in the present study the significant causes of death were given and not the primary cause, although it was recognized that a considerable degree of personal opinion was involved in deciding which conditions were significant.

The question of how much hyaline-like material had to be present in the lung in order to be considered a significant cause of death was admittedly decided on arbitrary grounds. This particular pulmonary lesion has been recognized as a cause of asphyxia and death in the newborn infant by all recent investigators,[2,7-11] but none has been able to determine under what conditions precisely it is a lethal factor. The same may be said for other pathologic conditions in the newborn including cerebral hemorrhage and pneumonia. It has been generally assumed that these were primary causes of death with little or no opportunity to obtain support for the assumptions from clinical studies. The considerable degree of uncertainty over the exact cause of death in a large number of newborn infants should not lead to the use of nondescript terms such as "congenital debility" and "prematurity." The pathologic conditions should be reported when found. When this is done, it will be found, as evidenced by the present study, that the incidence of serious pathologic conditions in the autopsy material on newborn infants is high. Knowledge of the incidence of these serious conditions should permit a more enlightened approach to the high mortality among newborn infants, particularly premature infants.

The terms "anoxia" and "asphyxia," which are given as leading causes of fetal and neonatal death by many, should not be used unless the causes of the anoxia or asphyxia are specified, since there is little agreement in recent reports as to what should be included under these terms. For instance, Macgregor[9] listed under "asphyxia" deaths from antepartum hemorrhage, prolapse of the cord and aspiration of amniotic sac contents, especially vernix caseosa. D'Esopo and Marchetti[12] described 22 conditions including toxemia of pregnancy as causes of "asphyxia," but did not distinguish between those causing fetal and neonatal deaths. Potter and Adair[13] were unable to specify the cause of the "anoxia" in almost one quarter of the cases so labelled by them and did not include toxemia of pregnancy as a factor in producing asphyxia. Labate[2] included only pulmonary conditions in the infant under "anoxia" and Assali and Zacharias[3] reported "asphyxia" as the sixth most frequent fetal factor causing infant deaths, but did not specify what the conditions were causing the asphyxia. Since most of the above investigators agreed that "anoxia" or "asphyxia" was the leading cause of fetal death and was a prominent cause of neonatal death, there should be better agreement as to which factors should be recognized as causing asphyxia.

Considerable advantage could be obtained if some formal agreement could be adopted by the obstetricians, pathologists and pediatricians as to how fetal and neonatal deaths

should be classified. The incidence of hospital deliveries is already high and continues to increase for the country as a whole. It is to be expected that this situation will increase the opportunities to carry out better and more clinical and postmortem examinations on newborn infants, which should serve as an added incentive for the adoption of some uniform plan of procedure for classifying fetal and neonatal deaths. The plan followed in the present study is not offered as a necessary or final solution to the difficulties, but does represent the author's efforts to point out that specific and serious clinical and pathologic conditions account satisfactorily for most fetal and neonatal deaths, while resorting to vague terminology and arbitrary opinion as little as possible.

Under the plan adopted in the present study, it was clear that the causes of fetal death were quite different from those which were considered as significant causes of death among live-born infants. In the former group, accidental interruption of the blood flow through the placenta or umbilical cord was the most frequently encountered cause of fetal death, while in the case of infants dying after birth usually some specific and significant pathologic condition was found which explained their deaths. These significant causes of neonatal death differed in the incidence with which they were observed in premature and full term infants.

The performance of a complete autopsy was an important factor in determining the significant causes of death in live-born premature infants who weighed between 1000 and 2500 gm. at birth. The presence of hyaline-like material in the lung and of cerebral hemorrhages, the two chief significant causes of death in this group of premature infants in this study, cannot be determined without microscopic studies of the lung and careful inspection of the cranial contents respectively. Failure to make these examinations in 7 of the 40 premature infants in this weight group who died accounted for most of the total group of infants dying of unknown causes in this study.

An interesting group of fetuses was made up of the 15 for which no significant cause of death could be found. The mothers of 8 of the 15 fetuses were over 35 years of age. A direct relationship between the age of the mother and fetal fatality rates has been demonstrated.[12] In view of the fact that a high fetal and neonatal mortality has been demonstrated among infants whose mothers developed diabetes mellitus after the age of 40 years and the fatality rates were definitely found to be increased when these women had passed 30 years of age,[14] the question can well be raised as to whether some of the unexplained fetal deaths among this older age group of mothers might not in some way be related to a prediabetic state which might or might not manifest itself years later.

Summary

An analysis of the significant causes of death in 4117 consecutive births was made; there were 66 fetal deaths and 85 neonatal deaths. A significant cause of death was determined in 51 fetuses and 56 live-born infants.

Eighty-five per cent of the live-born infants who weighed over 1000 gm. at birth and had postmortem examinations had causes of death which were considered to be significant. Almost half of the live-born premature infants with birth weights between 1000 and 2500 gm. were considered to have had more than one significant cause of death.

The so-called significant causes of death among live-born infants differed from those determined for fetuses dying before birth. Among the former, pathologic conditions in

the infants were determined four times more frequently than in those dying before birth and, in the latter, maternal complications of pregnancy and labor were diagnosed as significant causes of death five times more frequently than in infants dying in the neonatal period.

Hyaline-like material in the lung was considered to be the most frequent significant cause of death in live-born premature infants; congenital malformation and anoxia resulting from complications of labor were the most frequently determined significant causes of death in live-born full term infants. No differences were found in the significant causes of death in premature and full term fetuses. Anoxia resulting from accidental and unexpected interruption of the blood flow in the placenta and umbilical cord and from dystocia was the most frequently determined significant cause of death in both groups.

A plea has been made for the adoption by obstetricians, pathologists and pediatricians of a formal uniform plan of classifying the causes of fetal and neonatal death which would divest current efforts to determine the cause of death of as much vague terminology and arbitrary opinion as possible.

References

1. Dunham, E. C., Premature Infants, Children's Bureau Publication no. 325, Children's Bureau, FSA, Washington, D.C., 1948.
2. Labate, J. S., Study of causes of fetal and neonatal mortality on obstetric service of Bellevue Hospital, Am. J. Obst. & Gynec. **54**:188, 1947.
3. Assali, N. S., and Zacharias, L. F., Fetal and maternal mortality, Am. J. Obst. & Gynec. **54**:651, 1947.
4. Beck, A. C., Obstetrician's responsibility for hazards of first few days of life with special reference to anoxia and prematurity, Am. J. Obst. & Gynec. **51**:173, 1946.
5. Miller, H. C., and Hamilton, T. R., Pathogenesis of "vernix membrane" and its relation to aspiration pneumonia in stillborn and newborn infants, PEDIATRICS **3**:735, 1949.
6. Miller, H. C., and Jennison, M. H., Study of pulmonary hyaline-like material in 4117 consecutive births: Its incidence, pathogenesis and diagnosis, PEDIATRICS **5**:7, 1950.
7. Arey, J. B., Pathologic findings in neonatal period, J. Pediat. **34**:44, 1949.
8. Farber, S., and Sweet, L. K., Amniotic sac contents in lungs of infants. Am. J. Dis. Child. **42**:1372, 1931.
9. Macgregor, A. R., Pathology of stillbirth and neonatal death, Brit. M. Bull. **4**:870, 1946.
10. Johnson, W. C., and Meyer, J. R., Pneumonia in stillborn and newborn infants, Am. J. Obst. & Gynec. **9**:151, 1925.
11. Ahvenainen, E. K., On membranes ("vernix membrane") caused by amniotic fluid in lungs of newborn and on interstitial emphysema, as well as spontaneous pneumothorax, Ann. med. int. Fenniae **36**:367, 1947.
12. D'Esopo, D. A., and Marchetti, A. A., Causes of fetal and nonatal death, Am. J. Obst. & Gynec. **44**:1, 1942.
13. Potter, E. L., and Adair, T. L., Clinical pathological study of infant and fetal mortality for 10 year period at Chicago Lying-In Hospital, Am. J. Obst. & Gynec. **45**:1054, 1943.
14. Miller, H. C., Effect of prediabetic state on survival of fetus and birth weight of newborn infant, New England J. Med. **233**:376, 1945.

Spanish Abstract

Análisis de Muertes Fetales y Neonatales en 4117 Partos Consecutivos

Se hizo un análisis de las causas significativas de la muerte en 4117 partos consecutivos; hubieron 66 muertes fetales y 85 muertes neonatales. Una causa de muerte significativa fué determinada en 51 fetos y 56 infantes nacidos vivos.

Ochenta y cinco por ciento de los infantes que nacieron vivos pesando más de 1,000 gm. al nacer

y que tuvieron examenes después de muertos tuvieron causas de muerte que se consideraron ser significativas. Se consideró que la mitad de los infantes prematuros que nacieron vivos con pesos entre 1000 y 2500 gm. al nacer tuvieron más de una causa de muerte significativa.

Las causas de muerte llamadas significativas entre los infantes que nacieron vivos diferieron de aquellas determinadas para los fetos que murieron antes de nacer. Entre los primeros, las condiciones patológicas en los infantes fueron determinadas cuatro veces más frecuentemente que en aquellos que murieron antes del parto, y en los últimos las complicaciones maternales de embarazo y parto fueron diagnosticadas como causas de muerte significativas cinco veces más frecuentemente que en infantes que murieron en el período neonatal.

La sustancia parecida a la hialina en el pulmón se consideró como la causa de muerte más significativa en infantes prematuros nacidos vivos, la malformación congénita y la anoxia que resultan de las complicaciones del parto fueron las causas de muerte significativas más frecuentemente determinadas en infantes de término completo que nacen vivos. No se encontraron diferencias en las causas de muerte significativas en fetos de término completo y fetos prematuros. Se determinó que la anoxia que resulta de la inesperada y accidental interrupción de la corriente de sangre en la placenta y condrón umbilical y de la distocia fué la causa de muerte más significativa en ambos grupos.

Se ha hecho una petición para que los obstétricos, patólogos y pediátricos adopten un plan uniforme para clasificar las causas de muerte fetales y neonatales que descubran los esfuerzos actuales para determinar la causa de muerte de tanta terminología vaga y opinión arbitraria como sea posible.

University of Kansas Medical Center

ANALYSIS OF PREMATURE MORTALITY RATES

By EDWARD B. PLATTNER, M.D., ALBERT F. STEIN, M.D.,
AND HAROLD X. GERBER, M.D.
Chicago, Ill.

PREMATURE births occur more than five times in each 100 deliveries. Public Health Reports[1] cite an incidence of prematurity in 13,727 out of 255,727 deliveries. Peckham[2] reported 4055 prematures in 39,394 births at Johns Hopkins Hospital. Tyson[3] reported 2,960 prematures in 33,668 deliveries at Philadelphia Lying-in Hospital. Other investigators report incidences ranging from 3.25% by Wilcox[4] to 7.42% by Ritmiller and Nicodemus.[5]

Approximately half of all the neonatal deaths have been attributed to this infrequent complication of pregnancy. Reports from the U. S. Children's Bureau[6] indicate that 47% of all neonatal deaths were the result of prematurity. Wilson and Chesley[7] demonstrated that 52% of neonatal mortality of their cases was due to the premature onset of labor. Other authors (Grier and Lussky[8]) have reported that prematurity has been responsible for as high as 65% of the gross neonatal mortality.

During the years of 1941 to 1946, 2,910 prematurely born infants were treated in the Premature Station of the Children's Division of Cook County Hospital. An analysis of the mortality rates of this number of premature infants reveals information that may be of assistance in prognosticating the survival chances of small infants. This analysis will illustrate also the advantages of having specialized facilities, particularly nursing service, for the care of premature infants.

The relationship of mortality to birth weight has been demonstrated previously. Hess[9] analyzed 3883 cases at the Sarah Morris Hospital and reported the following mortality rates:

Birth weights of	*Mortality Rate*
Less than 1000 gm.	87.0%
1001 to 1500 gm.	49.9%
1501 to 2000 gm.	21.6%
2001 to 2500 gm.	11.0%
over 2500 gm.	8.9%

The mortality rate at Cook County Hospital is indicated in Table I. The relationship of survival to birth weight is re-emphasized in this table. The term "previable"[10] indicating birth weights under 1000 gm. needs re-examination. Of 165 premature infants weighing less than 1000 gm. at birth, 46 survived and were discharged weighing over 2.3 kg., a survival rate of 27.8%. The term "previable" is not applicable to this group when there is such a high survival rate.

The rapid decline in mortality as the birth weight rises is well known. This has been noted by Hess,[9] Dickman,[11] Einhorn,[12] and Flax, Levent, and Strong.[13] Examination

From Cook County Hospital, Chicago, Ill.
(Received for publication May 1, 1949.)

TABLE I

PREMATURES ADMITTED FROM 1941 TO 1946, INCLUSIVE

Birth wt. in gm.	Total no. admitted	Survivals	Deaths	Mortality per cent
0– 500	7	2	5	71.4
501–1,000	158	44	114	72.1
1,001–1,500	545	353	192	35.2
1,501–2,000	1,244	1,079	165	13.2
2,001–2,500	956	909	47	4.9
All wts.	2,910	2,387	523	17.9

of the mortality rate discloses that an infant weighing 1500 gm. at birth has a chance of surviving twice better than that of an infant weighing 1000 gm. or less. An infant weighing 1501-2000 gm. or 2001-2500 gm. at birth has a chance 5 and 14 times better, respectively, of surviving than has an infant weighing 1000 gm. or less. The implication of such figures is the value of prolonging pregnancy so the fetus may be as near term as possible at the time of delivery.

The influence of sex on the incidence of prematurity has been discussed. Grier and Lussky[8] reported 239 female and 214 male premature infants in a series of 453 cases. In the present series there were 1585 female and 1288 male premature infants (Table II). This is an incidence of 1.23 female infants to every 1.0 male infant. The mortality rates indicate that female premature infants do better than males. Only 15.3% of the female infants died in contrast to 21.9% of the male infants. There was a marked difference in the mortality rates of the two sexes in all the various groups of birth weights with but one exception, with that of the female being consistently lower than that of the male. There is no explanation for this higher mortality rate of male infants.

There were in this series 1660 nonwhite and 1247 white premature infants with mortality rates, respectively, of 15.7% and 20.6%. These rates suggest that the nonwhite infants have a better chance of surviving than the whites. The difference may be less, however, when some additional facts are presented. The mortality rate for 113 infants born in Cook County Hospital from 1943 to 1946 was 17.1%. The mortality rate for 803 infants transferred to the hospital after birth was 22%. But only 16% of the infants born at Cook County Hospital were whites, whereas 76% of those transferred to the hospital after birth were whites. Furthermore, a comparison of the mortality rates of the two groups transferred to the hospital after birth reveals a mortality rate of 21% for white and 25.3% for nonwhite prematures. These findings suggest that the important factor in the difference in the death rates of the two groups is the hazard of transferring premature infants from other hospitals or homes to Cook County Hospital. The difference in mortality rates for the two racial groups may be due to some racial characteristics.

The source of infants admitted to the Premature Station of Cook County Hospital since January 1, 1943 has been analyzed to determine the influence of transportation of premature infants on the survival rate. Two sources are considered: one from Cook County Hospital Maternity Division and from outside Cook County Hospital. There

TABLE II

PREMATURES CLASSIFIED ACCORDING TO SEX, COLOR AND BIRTH WEIGHT (1941–1946, INCLUSIVE)

Birth wt.	0–500			501–1000			1001–1500			1501–2000			2001–2500			TOTALS		
	Total	Deaths	Mort. %	Total	Deaths	Mort. %	Total	Deaths	Mort. %	Total	Deaths	Mort. %	Total	Deaths	Mort. %	Total	Deaths	Mort. %
Male	5	4	80	66	47	71.2	248	107	43.1	545	98	17.9	424	27	6.3	1288	283	21.9
Female	2	1	50	91	67	73.6	296	87	29.3	695	69	9.9	525	19	3.6	1585	243	15.3
White	3	2	66	64	48	75.0	241	104	43.1	557	74	13.2	382	29	7.6	1247	257	20.6
Nonwhite	4	3	75	93	66	70.9	306	88	25.4	687	91	13.2	570	14	2.4	1660	262	15.7

TABLE III

PREMATURES BORN IN COOK COUNTY HOSPITAL, CLASSIFIED ACCORDING TO SEX, COLOR AND BIRTH WEIGHT (1943–1946, INCLUSIVE)

Birth wt.	0–500			501–1000			1001–1500			1501–2000			2001–2500			Total		
	Total	Deaths	Mort. %	Total	Deaths	Mort. %	Total	Deaths	Mort. %	Total	Deaths	Mort. %	Total	Deaths	Mort. %	Total	Deaths	Mort. %
Male				23	14	60.8	111	46	41.4	221	42	19.0	143	9	6.2	498	111	22.2
Female				34	25	73.8	110	20	18.1	258	29	11.2	209	8	3.8	611	82	13.4
White				8	6	75.0	40	14	35.0	69	10	14.4	62	8	12.9	179	38	21.2
Nonwhite				49	33	67.3	183	51	27.8	412	61	14.8	290	8	2.7	934	153	16.3

TABLE IV

PREMATURES BORN OUTSIDE OF COOK COUNTY HOSPITAL, CLASSIFIED ACCORDING TO SEX, COLOR AND BIRTH WEIGHT (1943–1946, INCLUSIVE)

Birth wt.	0–500			501–1000			1001–1500			1501–2000			2001–2500			TOTAL		
	Total	Deaths	Mort. %	Total	Deaths	Mort. %	Total	Deaths	Mort. %	Total	Deaths	Mort. %	Total	Deaths	Mort. %	Total	Deaths	Mort. %
Male	2	2	100	26	19	73.0	59	24	40.6	177	33	18.6	108	12	11.1	372	90	24.1
Female	1	1	100	38	27	71.0	81	33	40.7	226	27	11.9	103	3	2.8	449	91	20.2
White	1	1	100	43	30	69.7	105	41	39.0	229	43	14.3	166	14	8.4	614	129	21.0
Nonwhite	2	2	100	21	16	76.1	35	16	45.7	90	13	14.4	41	1	2.4	189	48	25.3

were 1109* infants admitted from the Maternity Division (Table III). Of these 611 were female and 498 were male infants, an incidence of 1.23:1. The mortality rates for the male and female infants were 22.2% and 13.4%, respectively. The female infants had a greater survival rate than did the male in each of the groups of birth weights with but one exception.

Of the 1113* premature infants born in Cook County Hospital on whom the race was recorded 179 were white and 934 were nonwhite. The mortality rates were 21.2% for the white and 16.3% for nonwhite groups, respectively. The nonwhite infants showed a greater ability to survive than did the white in all of the birth weight groupings.

From January 1, 1943, to December 31, 1946, 821* premature infants were admitted to Cook County Hospital after birth to receive specialized care for small babies (Table

TABLE V

MONTHLY ADMISSIONS AND DEATHS FOR 1559 PREMATURELY BORN INFANTS
(1943–1945, inclusive)

		Jan.	Feb.	Mar.	Apr.	May	June	July	Aug.	Sept.	Oct.	Nov.	Dec.
1943	Admissions	46	40	66	41	50	56	66	40	42	35	39	37
	Deaths	10	10	20	13	8	15	13	7	7	7	15	11
1944	Admissions	42	45	40	45	36	60	42	37	46	58	44	42
	Deaths	8	10	14	4	10	13	6	14	7	17	7	10
1945	Admissions	47	38	33	40	36	48	43	33	35	31	25	55
	Deaths	15	11	6	15	13	16	6	11	9	11	5	11
TOTALS	Admissions	135	123	139	126	122	164	151	110	123	124	108	134
	Deaths	33	31	40	32	31	44	25	32	25	34	27	32

IV). Of these, 449 were female and 372 were male, an incidence of 1.21 female to 1.0 male. The mortality rates for male and female infants were 24.1% and 20.2%, respectively. The female infants had greater survival rate again then did the male infants in most of the groups.

Race was recorded on 803* infants transferred to Cook County Hospital after birth. There were 614 white and 189 nonwhite with mortality rates of 21% and 25.3% respectively. There was no consistency, however, in the various groups to indicate that the white infants had a higher survival rate over the nonwhite. The mortality rates for white infants in the birth weight groups of 501-1000 gm. and 1001-1500 gm. were 69.7% and 39.0% as compared with rates of 76.1% and 45.7% for nonwhite. But the mortality rate in the birth weight group of 2001 to 2500 gm. was 8.4% for the white infants as compared with that of 2.4% for the nonwhites. The rates were almost identical

* The discrepancy of these figures for the infants born on the Maternity Division is due to the failure of all the records to reveal the sex or the race. The sex was omitted more times than was the race.

in the other two birth weight groups even though the number of cases in the groups were different.

Comparison of mortality rates of premature infants born in the hospital with specialized care and with those born in other hospitals and transferred after birth indicates that there is a better chance for the survival if the infant is born in a hospital which has special facilities for this care. Only 17.4% of 1109 premature infants born in the hospital died. However, 22% of 821 infants born in hospitals or at home without facilities for their care died. Although 76% of the "outside" infants were white as compared with 16.1% of the "inside" babies, the difference in mortality rates in the "inside" and "outside"

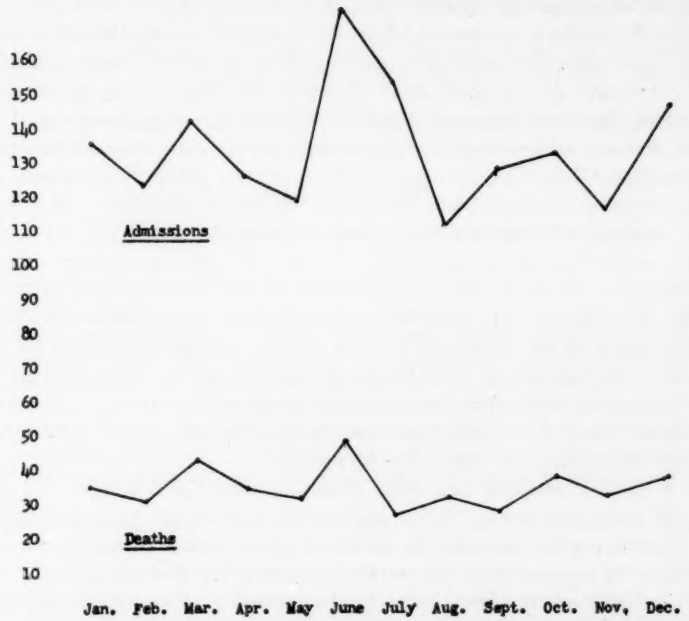

CHART I. Monthly Admissions and Deaths for 1569 Prematurely Born Infants (1943 to 1945 inclusive).

babies cannot be attributed entirely to race. This is considered to be so because there was a greater mortality rate for the nonwhite "outside" infants than for the white "outside" babies (25.3% and 21.0, respectively).

The important factor in the difference in the survival rates for premature infants born in the hospital and for those which are transferred from hospitals and homes without these facilities is the effect of the transfer itself. The premature infant is extremely delicate. During its first hours of life, it is in need of minimal handling, maintenance of the body temperature, provisions for adequate respiration (e.g., oxygen or gentle aspiration of mucus) and protection against infection. The delay in instituting these life-saving measures has undoubtedly contributed to the increased mortality of this group. The better general dissemination of knowledge in the care of premature infants would be of value in reducing the mortality rate.

The monthly incidence of prematurity was studied in 1559 infants (Table V) admitted

to the Premature Station between January 1, 1943, and December 31, 1945. It is seen that the monthly admissions vary between 31 and 66 infants, the average per month being 40.5. Although Einhorn[12] reported a higher incidence of prematurely born infants in August, September and October, the present study fails to reveal any consistent trends that indicate any month or months as being the time when prematurity has a more frequent occurrence. June and July had the largest number of cases admitted. However, the number of cases admitted in these months in different years is not consistently higher than that which occurred in other months of the same year. The number of infants admitted in June and July over the three year period is higher than that of any other month in the same three year interval.

Similarly the deaths of premature infants were studied from the viewpoint of monthly incidence. The number of deaths per month varied from 4 to 20 infants with an average of 10.7 per month. As was noted about the admissions, there was no month or months during which death occurred more frequently with any degree of consistency. There was a general tendency for the number of deaths to be high in those months when the admissions were high. There were 44 deaths in the three year period in the month of June. This was the same month that had the highest number of admissions, 164 infants. The monthly incidence of admissions and deaths is shown in Chart 1.

Summary

During the years of 1941 to 1946, 2,910 premature infants were admitted to the Premature Station of the Children's Division of Cook County Hospital. Of this number 17.9% died. The influence of birth weight on survival rate was demonstrated.

There were more female premature infants than males (1.23:1).

The female infants had a higher survival rate than the male infants (15.3% mortality rate for females as compared with 21.9% for males).

There were more nonwhite than white premature infants in this series. The nonwhite infants had a mortality rate of 15.7% whereas the white infants had a mortality rate of 20.6%. Possible explanations for this difference included racial factor and the factor of transportation of a prematurely born infant from one place to another.

Of the infants born at Cook County Hospital where the factor of transfer was nonexistent, nonwhite infants had a mortality rate of 16.3%; the white infants, 21.1%. Female infants survived better than did the male infants (female mortality rate, 13.4%; male mortality rate, 22.2%).

Of the infants transferred to Cook County Hospital, the white infants survived better than the nonwhite (21% as compared with 25.3%). The female infants in this group likewise showed greater survival ability as compared with the male infants (20.2% for females; 24.1% for males).

There was no month of the year in which prematurity was consistently higher than the other months.

The death of prematurely born infants likewise is not influenced by the month of the year. The mortality rate is related to the number of admissions and not to month or season.

References

1. Yerushalmy, J., Palmer, C. E., and Kramer, M., Studies in childbirth mortality, Pub. Health Rep. **55**:1195, 1940.
2. Peckham, C. H., Statistical studies on prematurity: Mortality of prematurity and effect of certain obstetric factors, J. Pediat. **13**:484, 1938.

3. Tyson, R. M., Fifteen year study of prematurity from viewpoint of incidence, mortality, and survival, J. Pediat. **28**:648, 1946.
4. Wilcox, D. A., Study of 330 premature infants, Am. J. Dis. Child. **52**:848, 1936.
5. Ritmiller, L. F., and Nicodemus, R. E., Analysis of 5-year incidence of premature births, Pennsylvania M. J. **47**:690, 1944.
6. Births, Infant Mortality, Maternal Mortality, Graphic Presentation, U.S. Dept. of Labor, Children's Bureau, Washington, D.C., Government Printing Office, 1943.
7. Wilson, V. O., and Chesley, A. J., Public health aspects of premature infant care in Minnesota, Journal-Lancet **61**:147, 1941.
8. Grier, R. M., and Lussky, H. O., Premature infant mortality, Am. J. Obst. & Gynec. **39**:669, 1940.
9. Hess, J. H., in Brennemann's Practice of Pediatrics, Hagerstown, Md., W. F. Prior Company, Inc., vol. 1, chap. 1.
10. Barnes, A. C., and Willson, J. R., Care of newborn premature infant, J.A.M.A. **119**:545, 1942.
11. Dickman, R. W., Neonatal deaths following term deliveries, 1937-1945, Minnesota Med. **29**:783, 1946.
12. Einhorn, M. B., Premature infant: Statistical study, New York State J. Med. **40**:1380, 1940.
13. Flax, L., Levent, E. L., and Strong, R. A., Study of premature mortality, J. Pediat. **21**:717, 1942.

SPANISH ABSTRACT

Un Análisis de las Proporciones de Mortalidad Prematura

De 1941 a 1946 se admitieron 2910 infantes prematuros en la Estación Prematura de la División de Niños del Cook County Hospital. De este número 17.9% murieron. La influencia del peso al nacer sobre la proporción de supervivencia quedó demonstrada.

Hubieron más infantes prematuros en las hembras que en los carones. (1.23:1).

Las hembras tuvieron una proporción de supervivencia más alta que los carones. (15.3% proporción de mortalidad para las hembras comparado con 21.9% para los varones).

Hubieron más infantes prematuros que no eran blancos que blancos en esta serie. Loa infantes que no eran blancos tenían una proporción de mortalidad del 15.7% mientras que los infantes brancos tenían una proporción de mortalidad de 20.6%. La explicación posible para esta diferencia incluyó el factor racial y el factor de transportación de un infante nacido prematuramente de un lugar a otro.

De los infantes nacidos en el Cook County Hospital, donde el factor de traslado no existió, los niños que no eran blancos tuvieron una proporción de mortalidad del 16.3%; los infantes blancos del 21.1%. Los infantes hembra sobrevivieron mejor que los infantes varones (la proporción de mortalidad en la hembra, 13.4%, la proporción de mortalidad en los varones, 22.2%).

De los infantes trasladados al Cook County Hospital los infantes blancos sobrevivieron mejor que los que no eran blancos (21% comparado con 25.3%). Los infantes hembra en este grupo también mostraron mayor habilidad de sobrevivir comparado con los infantes varones (20.2% para hembras; 24.1% para varones).

No hubo mes del año cuando la proporción de infantes prematuros fuera consistentemente más alta que otros meses.

La muerte de infantes nacidos prematuramente tampoco fué influenciada por el mes del año. La proporción de mortalidad está relacionada con el número de admisiones y no con el mes ni la estación del año.

1046 Wilson Avenue

EXPERIMENTAL USE OF METHYL TESTOSTERONE IN PREMATURE INFANTS

Preliminary Report

By JOSEPH N. SEITCHIK, M.D., AND HORST A. AGERTY, M.D.
Philadelphia

THE administration of androgens to experimental animals is followed by a marked decrease in the urinary excretion of urea, without alteration of the fecal nitrogen content. It has been demonstrated that this "retained" nitrogen is anabolized to tissue protein, as evidenced by the increase in kidney and muscle mass.[1] This nitrogen-sparing effect of the androgens has also been demonstrated in normal human subjects of all ages and in numerous pathologic conditions such as hypopituitary dwarfism, eunuchoidism, hyperthyroidism and Cushing's syndrome.[2]

Shelton and his co-workers have attempted to utilize the protein anabolic activity of the androgens in the treatment of premature infants.[3-5] These authors observed a more rapid weight gain and a general improvement in well being of infants treated with methyl testosterone.

It was the purpose of the present study to attempt to repeat this therapeutic experiment and, in addition, to measure the effect of methyl testosterone on the urinary excretion of nonprotein nitrogen in a small group of premature infants.

METHOD

Fifty-seven premature infants weighing between 1.3 and 2.3 kg. were included in the study. Thirty of these served as controls. The other 27 received methyl testosterone as crushed tablets in doses of 2.5 mg. twice daily.

The infants were weighed daily and the total nitrogen intake was carefully noted at each feeding. The formula offered to these prematures every 3 hrs. consisted of a powdered modified cow's milk derivative* in boiled water in a weight ratio of 1:8, respectively. In this manner all infants received a formula of identical composition given in quantity sufficient to satisfy them. Three infants in the 1.3 to 1.8 kg. group received calcium caseinate in their formulas.

The nonprotein nitrogen excretion was estimated in 16 male premature infants. Nine male infants formed the control group, averaging 2 kg. at birth. Seven male infants formed the experimental group, averaging 2.1 kg. at birth. A daily 8 hr. specimen of urine, collected from 8:00 a.m. to 4:00 p.m., was obtained. Specimens from each day of the 3 day test period were pooled. The total nonprotein nitrogen content of the urine samples was determined by the method of Rappaport and Eichhorn.[6]

Wt. gain of these infants was evaluated by 3 criteria: (1) the number of days required to regain birth weight; (2) the number of days required to attain 2.3 or 2.5 kg. (depending on the initial weight of the infant); (3) the percentage of birth weight attained during the period of study.

RESULTS

Inasmuch as the androgen dose-body weight ratio was considerably greater in the smaller infants, the cases were divided into 2 groups by weight, 1.3 to 1.7 kg. and 1.8 to 2.3 kg. The results obtained in both groups are similar (Table I).

From the Divisions of Pediatrics, Women, and Biological Chemistry, Hahnemann Medical College, Philadelphia, Pa.

(Received for publication April 27, 1949.)

* Similac®, M and R Dietetic Laboratories, Inc.

TABLE I

	Premature Infants (1.8–2.3 kg.)			Premature Infants (1.3–1.7 kg.)	
	Control	Methyl testosterone		Control	Methyl testosterone
No. of infants	24	19	No. of infants	6	8
Av. birth wt. (kg.)	2.1	2.1	Av. birth wt. (kg.)	1.6	1.5
No. of days to regain birth wt.	7.9	7.2	No. of days to regain birth wt.	9.7	10.0
No. of days to gain to 2.5 kg.	20.3	17.5	No. of days to gain to 2.5 kg.	27	27

TABLE II

	Premature infants (1.8–2.3 kg.)				Premature infants (1.3–1.7 kg.)			
Day of life	Av. % of birth wt.		Av. N intake gm./lb./3 days		Av. % of birth wt.		Av. N intake gm./lb./3 days	
	Control	methyl test.	Control	methyl test.	Control	methyl test.	Control	methyl test.
3–5	96.0	97.0	.469	.465	95.2	95.5	.483	.503
6–8	101.3	101.5	.704	.669	93.8	96.3	.613	.611
9–11	104.5	109.7	.799	.716	100.7	102.3	.845	.826
12–14	108.8	112.7	.903	.785	107.0	109.0	.888	.882
15–17	114.4	117.5	.943	.819	113.1	117.8	.969	1.062
18–20	119.6	124.2	.979	.823	119.5	125.6	1.085	1.071
21–23	125.8	127.7	.919	.786	126.8	131.4	1.081	1.045

TABLE III

	Av. % of nitrogen retained		Av. nitrogen intake gm./lb./3 days		Av. cc. in water retained/lb./3 days		Av. % of birth wt.	
Day of life	Control	methyl test.	Control	methyl test.	Control	methyl test.	Control	methyl test.
3– 4– 5	76	75	.450	.400	178	147	97	95
6– 7– 8	79	80	.600	.500	155	170	101	97
9–10–11	77	78	.680	.580	166	165	104	103
12–13–14	76	84	.760	.720	177	167	107	108
15–16–17	79	83	.810	.800	191	188	112	116
18–19–20	76	85	.860	.790	187	198	119	120
21–22–23	74	81	.840	.720	197	172	123	125

It is apparent from the average birth weight of the methyl testosterone-treated and control infants that they represent similar populations. The time required to regain birth weight, or an arbitrarily chosen weight (2.3 or 2.5 kg.), and the rate of weight gain are fairly similar in the control and experimental groups (Table II). While there is some suggestion that the infants treated with methyl testosterone showed a slightly more rapid rate of weight gain, the differences could not be considered clinically significant.

The excretion of urinary nonprotein nitrogen was expressed in terms of "percentage of nitrogen retained"

$$\frac{(\text{nitrogen intake-urinary NPN}}{\text{nitrogen intake}} \times 100).$$

These results have no significance as absolute values, inasmuch as fecal nitrogen was not measured. However, this calculation was utilized as a survey method whereby gross changes in urinary nitrogen excretion might be observed. This presumption appeared to be valid since urea is the prime urinary constituent influenced by androgen administration. In addition, the volume of fluid intake and urinary output was measured in this group of 16 infants. Water retained was expressed as the difference between intake volume and urinary output in cc./kg. body weight/3 day test period. These results are summarized in Table II. No difference in weight gain was observed between the control and experimental groups (Table III). The retention of water was similar. The percentage of nitrogen retained was slightly higher in the androgen-treated group. This difference, while minimal, appeared to be statistically significant (t-test). However, in view of the fact that proportionate doses of androgens in experimental animals, children and adults produce a marked decrease in the urinary excretions of urea, the difference observed here is of minimal clinical significance. Furthermore, the 8 hr. collection period is too brief to permit any conclusion when the differences are small.

Discussion

While the number of cases utilized in this study is admittedly small, the results indicate that in respect to the time required to regain birth weight, the number of days required to attain a weight of 2.3 or 2.5 kg. and the percentage of birth weight attained during this study, no striking differences between the androgen-treated and control groups could be demonstrated.

The "percentage of nitrogen retained" was slightly higher in the androgen-treated group. This difference appeared to be of minimal clinical significance.

These results are at variance with those previously reported. No significant protein anabolic effect of any clinical significance has been demonstrated in this group of infants. It is therefore apparent that adequately nourished premature infants do not respond to this growth stimulus. While there appears to be no experimental work available as to the ability of premature infants to absorb androgens from the gastrointestinal tract, it seems unlikely that they would experience difficulty in this respect.

All the infants whose urines were studied for nonprotein nitrogen excretion were males. Shay et al.[7] have demonstrated a greater protein anabolic effect of the androgen in female experimental animals. This sex difference may have played some minor role in limiting the response of the infants in this study to the methyl testosterone administered.

Summary

Fifty-seven premature infants weighing between 1.3 and 2.3 kg. were studied in respect to time to regain birth weight, time to attain an arbitrarily chosen weight and rate of weight gain. Twenty-seven infants received methyl testosterone. These infants demonstrated no evidence of growth stimulation.

In view of the meager metabolic effects of methyl testosterone in premature infants, there appears to be little justification for its use in premature infants.

Acknowledgments

The authors wish to thank Dr. Carl C. Fischer for his advice and criticism and Miss Dorothy Rush, R.N., and Miss Phyllis Wood, B.A., for their able assistance. The authors also wish to thank Roche Organon Co. for their generous supply of methyl testosterone (Neo-Hombreol®).

References

1. Kochakian, C. D., Effect of male hormones on protein metabolism of castrate dogs, Proc. Soc. Exper. Biol. & Med. **32**:1064, 1935.
2. Reifenstein, E. D., Jr., Protein-anabolic activity of steroid compounds in man, Philadelphia, Josiah Macy, Jr., Foundation, 1942.
3. Shelton, E. K., and Varden, E. A., Use of methyl testosterone in treatment of premature infants, J. Clin. Endocrinol. **6**:812, 1946.
4. Shelton, E. K., Varden, A. E., and Mark, J. S., Experimental use of methyl testosterone compounds in premature infants, J. Clin. Endocrinol. **7**:708, 1947.
5. Shelton, E. K., and Mark, J. C., Experimental use of testosterone compound in premature infants, California Med. **69**:339, 1948.
6. Rappaport, F., and Eichhorn, F., Microestimation of nonprotein nitrogen in serum, plasma or blood, Lancet **2**:171, 1947.
7. Shay, H. J., Gershon-Cohen, J., Paskis, K. E., and Fels, S. S., Influence of testosterone propionate on somatic growth in white rat, J. Endocrinol. **28**:877, 1941.

Spanish Abstract

Uso Experimental de Testosterone de Metilo en Infantes Prematuros; Informe Preliminar

Se estudiaron cincuenta y siete infantes prematuros que pesaban entre 1.3 y 2.3 kg. con respecto al tiempo de volver a ganar el peso de nacimiento, al tiempo de alcanzar un peso escogido arbitrariamente y proporción de aumento de peso. Veintisiete infantes recibieron testosterone de metilo. Estos infantes no dieron muestra de estimulación de crecimiento.

En vista de los escasos efectos metabólicos de la testosterone de metilo en infantes prematuros, parece que hay un poco de justificación para su uso en infantes prematuros.

235 North 15th Street

LONG BONE INVOLVEMENT IN SICKLE CELL ANEMIA

By JOHN R. ALMKLOV, M.D., ARILD E. HANSEN, M.D., PH.D.,
AND MARTIN SCHNEIDER, M.D., F.A.C.R.
Galveston, Texas

ROENTGENOLOGIC changes in the long bones of children with sickle cell anemia have not been commonly recognized. The occurrence of a pathologic fracture caused by the osseous derangement in this disorder has not been reported to date.

Herrick[1] in 1910 described the first case of sickle cell anemia. It was not discovered that this disease involved osseous tissue until 1924 when Graham[2] found changes in the long bones on autopsy. Cooley[3] in 1926 described a thick skull with a thin or absent outer table and perpendicular lines radiating outward from the inner table in a patient with this disorder. Three years later Moore[4] noted changes in the long bones.

ROENTGEN FINDINGS

Roentgenographic examination of the hands, feet and forearms of the 24 year old Negro male described by Moore[4] revealed a great decrease in the width of the medullary cavity because of the encroachment of the cortical bone. In some areas the medullary cavity was completely obliterated. Three other cases[5–7] of long bone changes due to sickle cell anemia were reported before Grinnan[8] described the first case in a child. In this 4 year old Negro female all the long bones had peculiar striations, a thin cortex and a widened medullary cavity. It is noteworthy that Caffey[9] in a study of 15 children with sickle cell anemia recorded none with long bone changes. Diggs, Pulliam and King[10] in an extensive study of 27 patients with sickle cell anemia found long bone involvement in 11 instances, but of the 9 patients under 12 years of age only one had such changes. The most common abnormalities in this series were abnormal trabecular markings, thickening of the cortex and narrowing of the medullary cavity with actual obliteration in some areas. There were also patchy areas of increased radiolucency. It is of interest that Diggs and coworkers as long ago as 1937 predicted that future studies would reveal pathologic fractures in patients with sickle cell anemia.

The youngest child to have osseous involvement of the extremities was an 8 month old Negro infant described by Danford, Marr and Elsey.[11] On the eighth day of the illness the roentgenographic examination was normal, but on the sixteenth day the fourth metacarpal on the right hand and second of the left showed irregular areas of decreased density. These changes disappeared 27 days later. Subsequently, two other case reports[12–13] have been made but both concerned adult subjects.

Macht and Roman[14] studied 48 patients with sickle cell anemia, 29 of whom were under 14 years of age. The long bones were examined in 35 cases with the following incidence of findings: widening of the marrow cavity, thinning of the cortex, and a coarsening of the trabeculae in 20 cases; periostitis in 6 cases; bone destruction in 3 cases; sclerosis of bone in 2 cases; and joint destruction in 2 cases. The periosteal changes which occurred were beneath long-standing leg ulcers.

From the Departments of Pediatrics and Radiology, University of Texas School of Medicine, Galveston, Texas.

(Received for publication April 27, 1949.)

Eleven of the 26 adult subjects studied by Legant and Ball[15] had generalized osteoporosis. There was one patient with osteosclerosis. Seven of the patients had patchy cortical thickening of the long bones and five had infarcts of the bones which were evidenced by translucent areas surrounded by a ring of sclerotic bone.

Pathology

The pathologic abnormalities in the long bones in sickle cell anemia were first described by Graham[2] in a 30 year old Negro male. The marrow cavity was reduced in size and at one point it was obliterated. The inner portion of the cortex consisted of a concentric lamellated structure with columns of dark red marrow alternating with layers of dense bone. The microscopic sections showed that the outer cortex was normal but the inner portion was invaded irregularly by spaces containing hyperplastic marrow tissue; sometimes this appeared within 1 mm. of the periosteal surface. In some areas the marrow cavity was filled with loose fibrous granular tissue. In others there were necrotic areas with hyaline material surrounded by lymphocytes and granulation tissue. Bone repair was also in evidence, and at times new bone formation proceeded so far as to narrow and distort or even obliterate the original marrow cavity. Diggs and coworkers[10] in their autopsy material on eight cases found that the cortex was thicker than normal and the density varied considerably in different parts of the same bone. The red marrow filled widened Haversian canals of the thickened cortex, giving it a honeycombed appearance. The marrow invasion of the cortex in some cases extended to the periosteum. New bone formation within the shafts of the long bones was the rule. Usually the form was that of delicate linear trabeculae but in some instances there were concentric layers of lamellated bone adjacent to the cortex and parallel to it or even thin sheets of bone perpendicular to the cortex. In some sections there was a complete replacement of the marrow cavity. Microscopic sections of the marrow revealed evidence of degenerative and reparative processes. Lesions found included thrombosis, infarction, necrosis, hemorrhage, granular and crystalline pigment deposits, hyalinization, fibrosis, abnormal calcification, and new bone formation.

Case Presentation

R.L.W., a 21 mo. old Negro male, entered the Negro Hospital of the University of Texas for his 2nd hospital admission. One month previously while sitting on his mother's lap in church someone lightly grazed his legs. This caused him to cry out suddenly. Following this episode he refused to stand and a warm tender swelling of his right thigh was noted.

First admission occurred at the age of 5 mos. because of severe sickle cell anemia. Weakness and jaundice were noted at 4 mos. of age. RBC count was 1.27 million and Hgb. 4.3 gm./100 cc. There were 65 nucleated RBC/100 white blood cells and, of course, sickling was present. Several blood transfusions were given. Subsequent to discharge he had 3 episodes of fever and irritability with swelling of ankles and hands. Family history is significant in that he had a sibling who died at the age of 7 mos. with a large spleen, the exact cause of which was not obtainable from the history.

Physical examination revealed a poorly nourished and poorly developed pale infant who refused to stand even when supported. Pulse 118, temperature 37.2°C., respiration 26 and blood pressure 98/68 mmHg. Wt. was 9.45 kg.; standing ht. was not recorded; head circumference was 47.5 cm. Muscle turgor was poor. There was swelling of the right thigh which extended from hip to knee. This area was firm, red, shiny, warm and tender. Right thigh measured 26.9 cm. in circumference and at a comparable point the left thigh was 16.2 cm. Lung fields were clear. There was a soft systolic murmur audible over the entire precordium. Liver and spleen were not palpable. No other significant findings were elicited.

Laboratory examination: Hgb. 4.5 gm./100 cc., erythrocyte count 1.53 million, leukocytes 24.8 thou-

sand with 55% neutrophiles, 13 nucleated RBC/100 white blood cells, positive sickling test, reticulocyte count 22.6%, platelet count 576 thousand, negative Kahn, serum albumin 3.56 gm./100 ml. and globulin 2.35 gm., serum phosphorus 5.05 mg./100 ml., serum calcium 9 mg./100 ml., alkaline phosphatase 5.89 Bodansky u., and acid phosphatase 2.2 Gutman u. Urinalysis was not remarkable. ECG was normal.

Survey of roentgenograms made at the time of admission revealed significant alterations in morphology of skull and long bones. The distal third of the right femur was the site of a comminuted fracture which displayed early callus and adjacent subperiosteal and soft tissue calcification (Fig. 1). Soft tissue swelling was prominent in the thigh. The fractured bone had an unusual "crumbled" appearance of the medulla. The medullary cavity of each femur was greatly widened and contained irregular calcific streaks consistent with old infarcts. All long bones displayed multiple transverse bands of growth disturbance.

The presence of calcification about the unhealed fracture site was consistent with a fracture about 3 wks. old. The severe comminution and medullary "crumbling," the extensive widening of the medulla, the paper-thin cortex of the distal third of the femur and the history of slight trauma, all led to the diagnosis of a pathologic fracture.

Follow-up films, 6 wk. later, of the right femur displayed progressive ossification of the callus and obliteration of the major fracture lines (Fig. 2). Slight shortening of the bone had occurred.

Other pertinent roentgenographic findings were (1) increased width with decreased density of some of the long bones, (2) increased thickness of the cortex of other long bones due to endosteal deposits of bone, and (3) structural changes of the frontal bone and of the facial bones (Fig. 3). The appearance of the latter was striking. There was reduplication of the inner table of the frontal bone; no radiating dense spicules were present. Generalized cardiac enlargement was evident on the chest roentgenogram.

FIG. 1. Initial roentgenogram of right femur. Comminuted fracture of distal third with severe soft tissue swelling, widened and decalcified medulla, thin cortex, "crumbling" of smaller central fragments and early calcification of callus and of hematoma. Latter indicates fracture of several weeks' duration. Irregular calcific streaks in medulla suggest old infarcts.

FIG. 2. Roentgenogram of right femur 6 wks. later. Well advanced ossification of callus, almost total obliteration of fracture lines, and some shortening of femur.

FIG. 3. Roentgenogram of lateral skull, thick frontal and facial bones with considerable diploic expansion and thick inner table in frontal bone. Bones, otherwise, are partly decalcified.

Patient was placed in Bryant's traction and remained there for 6 wks. He was permitted then to be up and around and seemed to enjoy walking about in his crib. He was discharged 2 mos. after admission.

DISCUSSION

Sickle cell anemia, Cooley's anemia and congenital hemolytic anemia have in common one special feature, a hyperplastic bone marrow. This develops because of the necessity of replacing destroyed erythrocytes. A widened medullary cavity with thinning of the cortex and prominent trabeculae may become apparent on roentgenographic examination. Vogt and Diamond[16] in 1930 pointed out that the roentgenologic features were similar in all three diseases. In sickle cell anemia, however, there are two processes going on at the same time. One is a hyperplasia of the marrow; the other is a thrombosis of the blood vessels in the bone. The latter feature is not present in the other two types of congenital anemias, hence there is a difference in the roentgenographic findings.

The thromboses of the vessels in the bone and marrow result in necrosis, hemorrhage, fibrosis, abnormal calcification and new bone formation. When this phenomenon occurs the new bone formation which results takes the form of linear trabeculae or concentric layers of lamellated bone adjacent to the cortex. This gives the roentgenographic picture of a wide cortex and thin medullary cavity and in some areas the medullary space is obliterated. The thickening of the cortex is irregular, which feature would be expected from the nature of the pathology. The thromboses of the vessels in the cortex produce infarcts with centers of decreased translucency surrounded by a ring of increased density,

or may produce patchy areas of increased density in the cortex. If thromboses occur near the surface of a joint, interference in function may result.

The findings on roentgenographic examination of the long bones in sickle cell anemia will depend upon which of the two processes is dominant—the hyperplasia of the marrow which produces a thin cortex or the sclerotic process which results in a thick cortex. Sometimes, as in the case described by Weil and Leiner,[13] both changes are present in the same bone. The sclerotic process tends to occur in the older age group. When bone changes are present in young children, usually they are of the hyperplastic marrow type with a thin cortex and widened medullary cavity. In this patient the sickle cell disease was severe and the onset of symptoms was at 4 months of age. Certain long bones showed a greatly widened medullary cavity which had caused so much thinning of the adjacent cortex that a pathologic fracture occurred. There have been a few cases of pathologic fractures reported in Cooley's anemia. Grinnan[8] had reported an 11 year old Italian girl with Cooley's anemia who had a pathologic fracture of both the radius and ulna. No instance of a pathologic fracture resulting from the bone changes in sickle cell anemia has been described.

Summary

Two types of pathologic changes may occur in the long bones of patients with sickle cell anemia. A hyperplastic bone marrow represents the response to continued destruction of erythrocytes and this produces a wide medullary cavity and a thin cortex. The thromboses of vessels in the marrow and bone result in abnormal areas of calcification and new bone formation producing a thick cortex and a small medullary cavity. The findings on roentgenographic examination will depend upon which of the two processes is dominant.

A 21 month old Negro infant whose symptoms of sickle cell anemia began at 4 months of age showed typical roentgenographic findings resulting from a hyperplastic marrow. The cortex in the femur had become so thin that a pathologic fracture resulted. This is the first reported instance of the occurrence of a pathologic fracture in sickle cell anemia.

References

1. Herrick, J. B., Peculiar elongated and sickled-shaped red blood corpuscles in case of severe anemia, Arch. Int. Med. **6**:517, 1910.
2. Graham, G. S., Case of sickle cell anemia with necropsy, Arch. Int. Med. **34**:778, 1924.
3. Cooley, T. B., and Lee, P., Sickle cell phenomenon, Am. J. Dis. Child. **32**:334, 1926.
4. Moore, S., Bone changes in sickle cell anemia with note on similar changes observed in skulls of ancient Mayan Indians, J. Missouri M. A. **26**:561, 1929.
5. Leivy, F. E., and Schnabel, T. G., Abdominal crises in sickle-cell anemia, Am. J. M. Sc. **183**: 381, 1932.
6. Brandau, G. M., Sickle cell anemia: Report of case, Arch. Int. Med. **50**:635, 1932.
7. Corrigan, J. C., and Schiller, I. W., Sickle cell anemia: Report of eight cases, one with necropsy, New England J. Med. **210**:410, 1934.
8. Grinnan, A. G., Roentgenologic bone changes in sickle cell and erythroblastic anemia, Am. J. Roentgenol. **34**:297, 1935.
9. Caffey, J., Skeletal changes in chronic hemolytic anemias (erythroblastic anemia, sickle cell anemia, and chronic hemolytic icterus), Am. J. Roentgenol. **37**:293, 1937.
10. Diggs, L. W., Pulliam, H. N., and King, J. C., Bone changes in sickle cell anemia, South. M. J. **30**:249, 1937.
11. Danford, E. A., Marr, R., and Elsey, E. C., Sickle cell anemia with unusual bone changes, Am. J. Roentgenol. **45**:223, 1941.

12. Kraft, E., and Bertel, G., Sickle cell anemia: Case report with unusual roentgen findings, Am. J. Roentgenol. **57**:224, 1947.
13. Weil, I. F., and Lerner, H. H., Case of long standing sickle cell anemia with marked bone changes, Am. J. Roentgenol. **60**:251, 1948.
14. Macht, S. H., and Roman, P. W., Radiologic changes in sickle cell anemia, Radiology **51**:697, 1948.
15. Legant, O., and Ball, R. P., Sickle cell anemia in adults: Roentgenographic findings, Radiology **51**:665, 1948.
16. Vogt, E. C., and Diamond, L. K., Congenital anemias, roentgenologically considered, Am. J. Roentgenol. **23**:625, 1930.

SPANISH ABSTRACT

Complicación del Huesa Largo en la Anemia Hematié

Pueden ocurrir dos tipos de cambios patológicos en los huesos largos de pacientes con anemia hematié. Una médula de hueso hiperplástica representa la respuesta a la destrucción continua de eritrocitos y esto produce una cavidad medular ancha y una corteza delgada. La trombosis de vasos en la médula y en el hueso resulta en areas anormales de calcificación y nueva formación de hueso que produce una cortesza gruesa y una cavidad medular pequeña. Los descubrimientos en el examen roentgenográfico dependerá en cual de los dos procesos es dominante.

Un infante negro de 21 meses de edad, cuyos síntomas de anemia hematié principiaron a los cuatro meses de edad, mostró hallazgos roentgenográficos típicos que resultaron de una médula hiperplástica. La corteza en el fémur se había vuelto tan delgada que resultó una fractura patológica. Este es el primer caso que se ha reportado de una fractura patológica en la anemia hematié.

University of Texas School of Medicine

COMPARISON OF NUTRITIVE VALUE OF MINERAL-ENRICHED MEAT AND MILK

By IRVINE MCQUARRIE, M.D., AND M. R. ZIEGLER, PH.D.
Minneapolis

THE nutritionist's dictum that every child should consume between one and two pints of milk daily to insure an adequate intake of calcium, sound as its basic concept may be, cannot, for various reasons, be applied universally. For instance, substitution of other foods is necessary for children who are allergic to milk proteins. Because of its carbohydrate content, milk is usually excluded in whole or in part from the diet of epileptic children when they are placed on the ketogenic dietary regimen as a therapeutic measure. Normal children may tire of milk after the period of infancy, and so fail to obtain an adequate amount of calcium to satisfy their needs unless suitable substitutions are provided. Milk is entirely available in many parts of the world to only a numerically insignificant percentage of the population after the weaning period.

For these reasons a substitute for milk as a source of calcium and phosphorus is highly desirable. While it has been demonstrated that the percentage utilization of Ca in dicalcium phosphate[1] and that in Ca-gluconate[2] is approximately the same as that of milk Ca, attempts to induce children to satisfy their Ca needs over long periods of time by consuming such salts directly in the form of flavored tablets rarely prove to be successful. On a dry-weight basis, certain green vegetables, such as spinach, chard and beet greens, are as rich in Ca as milk but they do not constitute a satisfactory food source of this element because much of the Ca is not assimilated.[3] Ca-oxalate of vegetables, for instance, is unutilizable.[4] Ca in fresh lettuce and string beans[5] and whole soy beans[6] is less available than that of milk, even when the vegetables are thoroughly cooked. The incidence of osteoporosis is high among children and adults in North China and other areas where the diet is composed largely of cooked green vegetables and soy bean products without any animal milk supplement.

Although Krane[7] ranked meat next to milk as a source of Ca in the human diet, it does not compare favorably with some other foods as a substitute for milk on the basis of its Ca content, unless cartilage and bone are included as they are to a considerable extent among certain Eskimo tribes.[8] One hundred grams of lean round beef, for instance, supplies a little less than one tenth the amount of Ca contained in 100 gm. of cow's milk. On the basis of protein content, the difference is still more extreme, the ratio of protein: Ca being 100:0.04 in lean meat and 100:3.5 in milk. Meat compares more satisfactorily as a partial source of P, the ratio of protein:P being 100:0.9 in lean meat and 100:2.7 in cow's milk.

Absorption of Ca from the gastrointestinal tract is largely dependent upon the solubility of its compounds and is related directly to the Ca to P ratio in the diet,[9] which is higher in meats than in vegetables.[10] It has been shown repeatedly that lactose differs from

From the Department of Pediatrics, University of Minnesota, Minneapolis, Minn.
Aided by a grant from the Medical Graduate Research Fund, University of Minnesota.
(Received for publication May 1, 1949.)

all other sugars in its favorable effect on the absorption and utilization of Ca and P in certain lower animals and in growing children.[11-15] Mitchell and co-authors[14] suggest that this attribute of lactose may depend upon its ability to maintain a higher hydrogen ion concentration throughout the intestinal tract. The values for percentage retention of Ca by five boys ranging in age from 5 to 7 years were found by Mills and collaborators[15] to be 33.5% higher during lactose than during nonlactose periods.

The experimental and clinical studies reported here were designed to compare the nutritive value of Ca and P-enriched meat with that of whole cow's milk as a principal source of protein, Ca and P in the diet. A preliminary report on a portion of the data to be presented has already been published.[16]

TABLE I

CHIEF COMPONENTS OF MILK AND OF BASIC MEAT DIETS

Constituents	Amounts (gm.)	Composition (gm.)							
		Prot.	Fat	CHO	Ca	P	Mg	K	Water
A. MILK DIET									
Whole milk (cow's) dried	65	17	18.0	24.5	0.57	0.44	0.06	0.68	1
Dextrin	26			26.0					
Water	82								82
Totals	173	17	18.0	50.5	0.57	0.44	0.06	0.68	83
B. BASIC MEAT DIET									
Strained beef*	100.0	17	2.0		0.01	0.14	0.02	0.34	80
Butter fat	15.6		15.6						
Dextrin	50.5		50.5						
Ca-gluconate	6.3				0.56				
KH_2PO_4	1.3					0.29		0.34	
Mg citrate	0.4						0.04		
Totals	174.1	17	17.6	50.5	0.57	0.43	0.06	0.68	80

* Swift and Company.

PLAN OF EXPERIMENTS AND METHODS AND MATERIALS USED

The investigation consisted of 2 parts, a more extensive experimental study relating to the effects of various diets on the skeletal metabolism and the total body growth of rats and a short balance study on 2 adolescent boys.

That part of the investigation which was designed to compare the rates of growth and the retentions of Ca and P by animals reared on the various test diets was carried out as follows: Young rats weighing between 58 and 67 gm. were divided into 2 similar groups. They were kept in individual cages. One group was given a diet in which milk was the sole source of protein, Ca and P. The other was given a synthetic diet made up to contain the same amounts of protein, fat, carbohydrate and minerals as milk but with strained meat (finely divided, cooked lean beef) as the only source of protein.* The composition of the basic meat diet, as well as that of the milk formula, is shown in Table I. Ca-gluconate, monobasic K-phosphate and Mg-citrate were added to the meat diet in

* The strained meat used was furnished by Swift and Company at our request.

amounts sufficient to make the final mixture contain essentially the same amounts of Ca, Mg, K and P as milk. (Swift's "Meat for Babies" contains added NaCl in amounts sufficient to satisfy the taste of the average person.)

Both diets were supplemented with vitamins as follows: cod liver oil, 0.5%; wheat germ oil, 0.8%, and choline chloride, 0.1% of the dry weight. These vitamins were added directly to the mixed diet. The other vitamins required were fed daily in caster cups at the following levels: thiamine hydrochloride, 80 mg.; riboflavin, 160 mg.; Ca-pantothenate, 100 mg. and niacin, 150 mg. Dextrine was the carbohydrate used in the meat diet in all rat experiments excepting one in which it was partially replaced by lactose, the amount of the latter sugar being equivalent to that in milk. To equalize the carbohydrate in the 2 diets, some dextrin was added to the milk diet.

Because the meat-fed rats receiving lactose showed early a tendency to diarrhea, finely shredded quantitative filter paper was added to this diet. Four gm. of paper to 100 gm. of the diet (dry weight) proved to be effective in preventing diarrhea. Three groups of animals were maintained on the enriched meat diet and 3 on the milk diet for 6 wks. Another group in each category was kept on the diet for 8 wks. A smaller number of rats maintained on a presumably complete stock diet (Champion rat food) served as an over-all control group.

With the hope of determining the range of need for additions of Ca and P to the meat diet, feeding experiments were carried out on small series of rats with (a) no additions of these elements, (b) with Ca addition only, and (c) with P additions only for final comparison with results from adding both in quantities equivalent to those in milk.

All food was offered each day in the same semisolid form in excess of what was consumed. Water was likewise allowed *ad libitum*. The constituents of the basic meat diet and milk diet are presented in Table I. The stock diet differed from the others in several respects, the protein being 31%, carbohydrate 48, fat 8, Ca 0.97, and P 0.9% of the dry weight.

All animals were weighed at regular intervals and note was taken of their consumption of food, their appearance and their activity. At the end of the experimental period they were fasted for 24 hrs. with free access to water only. They were then killed by decapitation. Blood samples from individual rats in each group were collected at this time and pooled for serum Ca, P and protein analyses. Ca and P were determined by the methods of Clark and Collip[17] and Kuttner and Cohen,[18] respectively. Proteins were determined by Howe's[19] fractionation followed by the micro Kjeldahl technic of Ma and Zuazaza.[20]

The whole carcass of each animal was weighed, then ground to a fine homogeneous mass, dried in an oven at 110°C. and ashed in a muffle furnace at 450°C. The ash was then analyzed for Ca[21] and P.[22] In some animals the right femur was carefully dissected out, freed from all soft tissue, weighed, dried in an oven at 110°C., and ashed by the process proposed by Gabriel and modified by Morgulis.[23]

The second phase of the study consisted of measuring N, Ca and P balances of growing subjects, (a) when they were maintained on ordinary mixed diets with milk as the principal source of protein and practically the only source of Ca and P and, (b) subsequently when finely ground lean beef enriched with Ca and P was substituted for milk in amounts providing the same quantities of protein and the 2 mineral elements.

The experimental subjects were 2 handicapped boys, the only ones available. H.D., aged 14 yrs., wt. 45 kg., suffered from residual paralysis of the lower extremities from poliomyelitis contracted 2 yrs. previously. C.M., aged 12 yrs., wt. 33 kg., was partially incapacitated by chronic, progressive muscular dystrophy. Both were semiambulatory and had been in the University of Minnesota Hospital for a number of weeks receiving essentially the same form of physiotherapy before the balance studies were begun in the special metabolism ward. Both had been given the regular, mixed hospital diet for adolescents in whatever amounts satisfied their appetites supplemented by approximately a pint of milk daily as well as extra orange juice and vitamins A and D. They were allowed to take the special diet in each instance 1 wk. before quantitative collections of urine and feces were begun. Each served as his own control in the comparison of results from the 2 types of feedings, first taking the milk diet and then the modified meat diet. The constituents of the diet were given on a basis of unit of body weight and both consumed the food satisfactorily. Each subject was given 2.35 gm. protein, 2.79 gm. fat, 7.36 gm. carbohydrate, 0.044 gm. Ca and 0.041 gm. P/kg. body wt./day. This provided a Ca:P ratio of 1.07:1. The period on each diet was approximately 3 wks., quantitative data on the intake and output being collected during the last 2 wks. of each period only. Standard

methods for marking and collecting stools and urine and for determining N, Ca and P were used. Roentgenograms of the long bones showed a mild degree of generalized osteoporosis in C.M., the subject with progressive muscular dystrophy. The essentially normal boy, W. D., showed entirely normal calcification, except for a mild decrease in density of the bones of the lower extremities, due perhaps to enforced inactivity. The Ca allowances in the diets of these subjects was somewhat above that ordinarily recommended, not only because of the mild osteoporosis, particularly in the younger boy, but also because both children were in the age period of rapid growth.[24]

Results

The results of the various phases of the study are presented with the aid of a series of graphs and tables which summarize the detailed data. Although all experimental data, excepting those on the

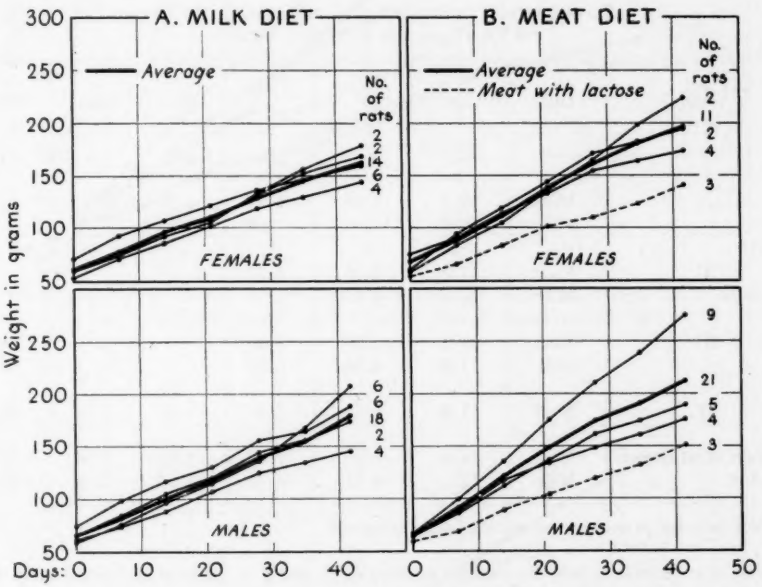

Chart 1. Growth curves of rats reared on: A. milk diet; B. basic meat diet of similar composition.

serum of rats, were obtained for individual animals, group averages alone are represented to save space. The variation of individual responses within groups was not sufficiently significant to justify reporting of individual data.

Growth Studies

Growth curves of young rats maintained on the milk-simulating (Ca- and P-enriched meat) diet are shown in Chart 1 for comparison with those of controls fed a diet in which milk was the sole source of protein, Ca and P. Curves for females are kept separate from those of males. The different lines represent the averages for different small groups of animals placed on the study at different times. Only among the meat-fed male animals does one group appear to outstrip the others in growth significantly. The explanation for this is not apparent.

It is obvious that the growth of the meat-fed rats (both male and female groups), receiving a portion of their carbohydrate as lactose, is inferior to that of both the milk-fed and the other meat-fed animals. The cause of this retardation is obscure. The animals consumed their diet and showed no diarrhea when shredded filter paper was mixed with the diet. What appears to be a species

intolerance on the part of the rat to artificially prepared lactose has been observed by other workers. However, comparison of the average growth curves of rats (both male and female) fed on the meat diet (exclusive of those receiving lactose) with those on the milk diet indicates no superiority of the latter. In fact, the meat-fed rats consistently grew at a slightly greater rate than the milk-fed rats.

Results of analyses of blood serum of the various groups of meat-fed and milk-fed rats are recorded in Table II. Except for the excessively high levels for serum P in both the meat-fed and milk-fed animals of the first group of rats tested all values are considered to be normal. The aberrant P values referred to may be explained by the fact that pooled blood samples were both found to be hemolysed. As indicated in the last 2 lines of figures in the table, which represent average values for all animals in the 2 separate categories, there is no significant difference between them.

TABLE II

Ca, P AND PROTEINS OF SERUM FROM SAMPLES OF BLOOD POOLED FOR EACH GROUP OF RATS (Per 100 ml.)

Group	Diet	Ca	P	Total Proteins	Alb.	Glob.	NPN
		mg.	mg.	gm.	gm.	gm.	mg.
I	Meat	10.4	11.8*	7.38	4.37	2.81	
	Milk	10.8	11.6*	7.09	4.57	2.52	
II	Meat	11.2	6.06	6.89			
	Milk	12.0	6.60	6.75			
III	Meat	12.2	6.00	7.16			29.4
	Milk	11.0	6.06	6.79			32.6
IV	Meat	11.8	6.84	6.58	3.53	3.05	34.8
Average of all rats on 1 diet	Meat	11.4	6.30	7.00	3.95	2.98	32.1
	Milk	11.2	6.33	6.87	4.57	2.52	32.6

* Not included in average for all rats; same hemolysis.

Since it is feasible to vary the absolute amounts of Ca and P in the meat diet considerably without altering its palatability significantly, it was deemed advisable to determine whether some other ratio of Ca:P than that in milk might alter the nutritional value of the mixture. Using the amount of Ca occurring in whole cow's milk (per unit amount of protein) as a practical standard of reference, different levels of P were tested. One group of 10 rats was given the basic meat diet (same protein, Ca and P content as milk) plus sufficient additional P to provide a Ca:P ratio of 1:1. Another group of 10 rats was given the basic meat diet minus the added P in order to determine whether the considerable amount of this latter element which occurs naturally in lean meat (approximately 40% of that in milk) might be adequate. The Ca:P ratio in this diet was 3.37:1. A 3rd group of 10 rats was given a meat diet containing the same amount of added Ca as the others but with an amount of P added sufficient only to provide a Ca:P ratio intermediate between this and that of the basic meat diet, namely 2.36:1. These were all compared with 4 rats raised on the stock diet, which, however, is admittedly not comparable because its basic composition differs materially in several other respects than its Ca and P contents from the diets under investigation.

Comparisons between the composite growth curve of 17 rats on the milk diet and that of 18 rats on the basic meat diet (as shown in the previous figure), on the one hand, and the average curve for rats on the basic meat diet without the added P (i.e., Ca alone added to meat), on the other, indicates that this latter diet is defective. (See Chart 2.) The growth curve characteristic of the group on the low P diet practically coincides with that of rats on the basic meat diet which was modified by substitution of lactose for part of the dextrin to simulate milk more closely.

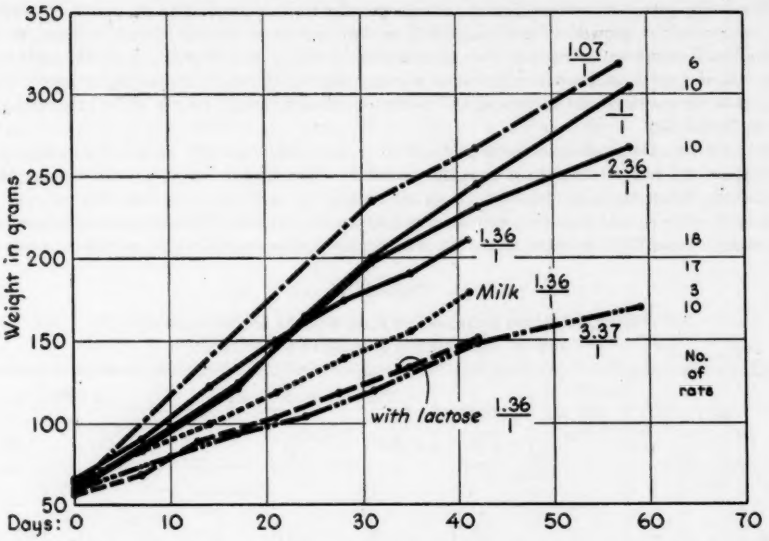

CHART 2. Growth curves of male rats reared on meat diets with varying Ca:P ratios compared with growth curve of similar animals reared on milk diet.

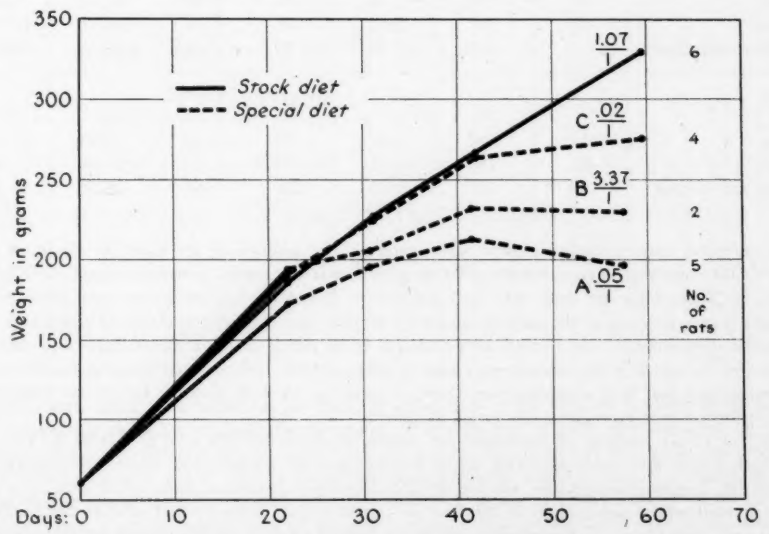

CHART 3. Growth curves of half-grown male rats as affected by substituting for stock diet: A. meat diet unenriched with Ca or P; B. meat diet enriched with Ca alone; C. meat diet enriched with P alone.

The other curves shown in Chart 2 indicate that the relative amounts of Ca and P in milk may not be optimal for growth. It would appear from these results, at any rate, that a moderate decrease as well as a significant increase in P level compared to that of milk may be compatible with a suitable rate of growth under the conditions of this experiment. The slight superiority of growth of the 4 animals on the stock diet may be related to the comparatively high protein (30%), as well as Ca and P, in that diet.

The effects of meat diets deficient in Ca or P or both on the growth curves of rats maintained throughout the first third of their growing period on a presumably adequate stock diet are shown in Chart 3. When the meat diet, without any addition of Ca or P, was substituted for the stock diet of 5 half-grown normal rats, their weight curve (A) showed evidence of beginning retardation within less than 10 days. This evidence of growth failure became more marked as the period of observation

TABLE III

WHOLE CARCASS ANALYSES OF RATS REARED ON (a) MILK DIET AND (b) MEAT DIETS OF SIMILAR COMPOSITION

Diet	No. of rats	Body wt. gm.	Per cent of wet body wt.			Per cent of ash	
			Ash	Ca	P	Ca	P
		FEMALES					
Milk	12	151	4.09	1.21	0.69	29.41	17.00
Meat	6	187	3.85	1.12	0.59	29.08	15.22
Meat with lactose	3	120	3.77	1.07	0.63	28.38	16.71
		MALES					
Milk	11	174	3.94	1.10	0.61	27.95	15.66
Meat	10	191	3.47	1.06	0.57	30.70	18.20
Meat with lactose	3	130	3.88	1.10	0.64	28.35	16.49
		MALES AND FEMALES					
Milk	23	162	4.01	1.15	0.65	28.71	16.35
Meat	16	189	3.61	1.08	0.58	30.09	17.08
Meat with lactose	6	125	3.82	1.08	0.63	28.36	16.60

was extended until arrest of growth was complete. The addition of Ca alone to the meat diet (curve B) was little, if any, better so far as growth was concerned, the same shaped curve being obtained. Substituting the meat diet with addition of P, but no Ca, appears to have produced no change in the direction of the growth for the 1st 20 days, but thereafter evidence of retardation was manifest. Unfortunately, no animals were available to be placed on the complete basic diet enriched with both Ca and P in the amounts necessary to simulate milk. It is obvious, however, from the data recorded here that both elements must continue to be supplied in amounts far greater than those in unenriched meat throughout the period of growth.

Whole carcass analyses of litter-mate rats reared on either the milk type of diet or the Ca- and P-enriched diet were made according to the methods already outlined. The results are presented in Table III. The enriched-meat-fed rats are divided into 2 groups because those which received a portion of their added carbohydrate in the form of lactose did not grow as well as those not receiving this sugar. (See Chart 1.) Figures recorded for the different groups are the averages of all individual analyses in those groups. Because of possible differences due to sex, such as body size, data for males and females are tabulated separately.

The body weights of animals reared on the Ca- and P-enriched meat without lactose were consistently slightly higher than those fed on the milk diet, but the percentages of total ash and Ca

in the wet carcass tended to be only slightly higher on the average in the milk-fed. While the meat-fed rats, which received lactose, were significantly lighter in weight than the other animals, the percentages of ash, Ca, and P were of the same magnitude. It is fair to interpret these data as indicating little or no important metabolic differences between the milk-fed and the modified meat groups except for the slowed rate of growth of the meat-fed rats which received lactose.

The average results of analyses of a single femur from each animal in the various dietary groups are recorded in Table IV. Certain differences in the skeletal metabolism among the different groups are apparent. The total or wet weight of the femur, the organic matter, the fat free dry weight, the ash, and the Ca:P ratio of the ash were all consistently, though perhaps not significantly, lower in the rats reared on the milk diet than in those fed the basic meat diet enriched with Ca and P to simulate the composition of milk. Comparison of the size and composition of the femurs of meat-fed

TABLE IV

Ca, P and Organic Matter of Femurs of Rats Fed (a) Milk, (b) Modified Meat and (c) Stock Diets (Expressed as group averages of individual analyses)

Animals			Diet				Femurs						
No. in group	Average body wts.		Type	Percentage of			Wet wt.	Organic matter	Fat free dry wt.	Percentage of FFD wt.		Ash	
	Initial	Final		Ca	P	Ca/P				Ca	P	Total	Ca/P
	gm.	gm.					mg.	mg.	mg.			mg.	
11	67	198	Milk	0.567	0.416	1.36/1	583.2	114.5	330.6	25.34	10.44	212.1	2.23/1
15	67	226	Meat	0.567	0.416	1.36/1	673.8	142.9	349.4	27.50	11.29	226.0	2.43/1
10	59	171	Meat	0.567	0.168	3.37/1	442.8	146.1	295.7	17.76	7.95	169.0	2.26/1
10	59	267	Meat	0.567	0.239	2.36/1	855.4	215.4	501.1	19.22	9.45	302.3	2.00/1
10	59	294	Meat	0.567	0.567	1/1	869.1	217.7	524.5	18.10	9.76	320.5	2.07/1
6	59	329	Stock	0.970	0.900	1.07/1	1011.7	235.9	593.5	19.90	9.68	372.9	2.05/1
5	172	196	Meat	0.008	0.168	0.05/1	690.9	148.9	317.6	11.96	6.67	126.5	1.78/1
4	194	277	Meat	0.008	0.416	0.02/1	816.3	309.7	409.3	8.55	5.49	128.4	1.58/1
2	193	229	Meat	0.567	0.168	3.37/1	995.8	157.2	515.0	19.86	12.23	391.8	2.07/1

animals show fairly wide variations according to differences in the absolute amounts of Ca and P in the diet and the ratios of Ca:P. Of the groups of animals fed the meat diet containing the same amount of Ca as milk on a protein to Ca basis but varying amounts of P, that group receiving the diet with no added P (Ca:P 3.37:1) showed the most profound deficiency in bone metabolism. The total weight, the fat free dry weight, the ash, and the percentage of both Ca and P in the fat free dry substance were far below those of the other groups, although the Ca:P ratio in the ash was almost identical with that of the rats fed the milk diet. Oddly, the group of animals in this series which were fed a meat diet with a Ca:P ratio of 2.31:1 and the group with a 1:1 ratio showed little difference in all measurements. The total wet weight of the femur, the organic matter, the fat free dry weight and the total ash were greater in those animals than in those of the earlier series which were fed on the diet which simulated the composition of milk more closely. However, the

percentage of Ca and of P in the bone was distinctly lower than that in the other series. The absolute amounts of Ca and of P were practically the same in the femurs of these rats and those of the rats reared on the basic meat diet with a Ca:P ratio of 1.36:1. The animals kept on the stock diet showed growth of bone superior to that of all other groups and composition similar to that found in the rats reared on the meat diets with Ca:P ratios of 1:1 and 2.36:1.

Of the 3 groups of half-grown stock rats which were placed for 6 wks. on the meat diet (A) without addition of either Ca or P, (B) with addition of Ca only, and (C) with addition of P only, the Ca-supplemented group alone showed femur size and composition similar to those of rats fed from the beginning on the meat diets with both elements added. While the total body growth of the animals fed the meat diet with added P was superior to that of the Ca-supplemented group, the deposition of both Ca and P was defective in the extreme while the organic matter was present in

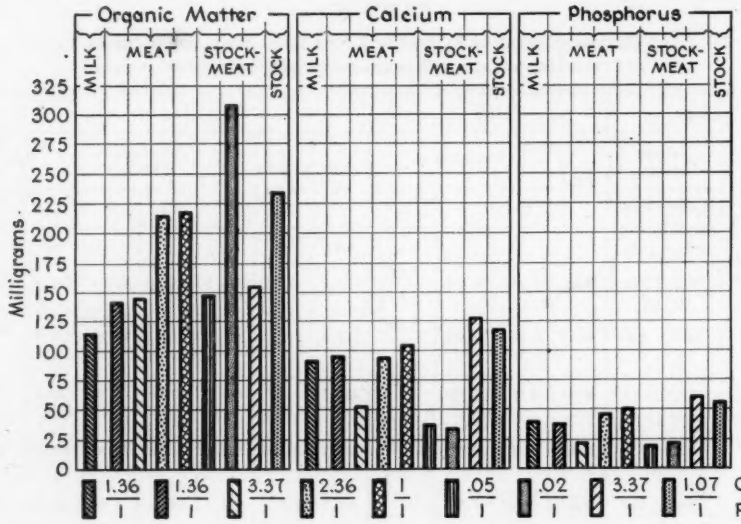

CHART 4. Analyses of femurs of male rats reared on meat diets with varying Ca:P ratios compared with analyses of femurs of similar animals reared on milk diet.

excessive amounts. The Ca:P ratio of the ash of these animals was the lowest encountered, namely, 1.58:1. Finally, the group of rats receiving no additions of either element showed not only extreme retardation in general body growth but also extensive losses of Ca and P from the skeleton. The Ca and P in the residual ash were present in a ratio of 1.78:1. (See Chart 4.)

BALANCE STUDIES ON HUMAN SUBJECTS

The results of N, Ca and P balance studies on 2 adolescent boys are summarized in Table V. The subjects were first maintained for 3 wks. on the milk-containing diet and then for a similar period of time on the same mixed diet but with Ca- and P-enriched lean meat substituted for the milk. Collections of urine and stools were made during the last 16 days of each period in the case of H.D., and during the last 14 days of each period in the case of C.M. Both diets were taken well throughout the entire period of study by both subjects.

There was a striking similarity between the data obtained for the milk and meat dietary periods in the case of each boy. As regards N excretion, it may be observed that the daily average amount lost in the feces was more than 50% greater for each boy on the meat diet than on the milk diet, but a lesser amount was excreted in the urine. A positive N balance was found for both boys on both diets. The magnitude of the positive balance for both subjects was slightly greater during the meat period.

Despite the fact that the Ca intake was considered to be well above the minimal requirements, there was a consistently negative balance of this element in the case of each boy on both diets. This was slightly more marked for the period of the milk diet than for that of the meat diet.

The P balance, like the N balance, was slightly positive for both subjects on both of the diets. Again the degree of retention was measurably greater in the case of the meat diet.

The Ca, P and protein of the blood serum of both boys were within the range of normal at the beginning of the short period of study and remained so. There was no significant change in the body weight of either boy.

TABLE V

COMPARISON OF N, Ca AND P BALANCES OF TWO ADOLESCENT BOYS WHEN MAINTAINED ON STANDARD DIET WITH MILK AS SOLE SOURCE OF PROTEIN WITH THOSE OF SAME SUBJECTS AFTER SUBSTITUTION OF Ca- AND P-ENRICHED MEAT FOR MILK

Subject	Type of diet	Metabolite	Intake	Output		Balance
				Urine	Stool	
			gm.	gm.	gm.	gm.
H. D.	Milk		16.94	12.74	1.09	+3.11
Age 14	Meat		16.94	11.78	1.76	+3.40
Wt. 45 kg.		N				
C. M.	Milk		12.42	9.80	0.93	+1.69
Age 12	Meat		12.42	8.54	1.44	+2.44
Wt. 33 kg.						
H. D.	Milk		2.01	0.14	2.06	−0.18
	Meat		2.01	0.13	1.96	−0.08
		Ca				
C. M.	Milk		1.47	0.16	1.48	−0.17
	Meat		1.47	0.10	1.49	−0.12
H. D.	Milk		1.86	0.71	0.89	+0.25
	Meat		1.86	0.90	0.65	+0.31
		P				
C. M.	Milk		1.36	0.53	0.75	+0.08
	Meat		1.36	0.57	0.60	+0.18

DISCUSSION

It is obvious from the foregoing experimental data that lean meat appropriately enriched with Ca, P, carbohydrates and certain vitamins is nutritionally equal to cow's milk (also supplemented with carbohydrate and certain vitamins), as judged by body growth and bone composition in rats and by N, P, and Ca balance studies in two adolescent boys. The true significance of the small differences in response to the two types of diet, which appear to indicate some degree of superiority of the meat diet, cannot be accurately appraised until more extensive investigations have been made. The character of the furry coat, the turgor of the tissues, and the spontaneous motor activity of the experimental animals at the end of the period of observation were essentially identical in the milk-fed and the meat-fed rats.

In the course of an investigation on the effect of an extremely high protein intake on antibody formation during the first few months of life, our associates, Adams, Kimball and Adams,[25] found that infants between the ages of 2 and 4 months thrived on comparatively large supplements of strained lean meat (Swift and Company "Baby

Meats"). Since milk constituted the major portion of the total diet, providing approximately half of the total protein given, it may be assumed that it supplied sufficient amounts of Ca and P to meet the infant's basic requirements for these elements. Sisson and associates of the University of Rochester (unpublished data) more recently found that premature infants thrived as satisfactorily on a meat plus milk formula, or even on the Ca- and P-enriched strained meat formula used in our preliminary experiments,[16] as on a standard milk formula, containing the same amounts of protein, fat and carbohydrate.

The experimental data presented in the present report indicate very clearly, however, that meat alone or meat enriched with but one of the bone forming mineral elements is not an adequate substitute for milk. When used to replace the major portion or all of the milk in the diet, as in the case of an infant or young child who is strongly allergic to milk proteins, the finely ground, cooked meat should be enriched with both Ca and P in amounts approximating those supplied by milk. Obviously, other supplements such as carbohydrate and certain vitamins (particularly A, D, and C) must be added as in the case of a cow's milk formula. Lean meat is a good source of thiamine and riboflavin and an excellent source of iron. Fat in the form of lard, beef fat or butter fat may be added to make the total fat content comparable with that of milk, if necessary to insure an adequate caloric intake.

The comparatively short study of N, P and Ca balances in the two boys does not constitute a wholly conclusive test. Nevertheless, the results are consistent in showing the Ca- and P-enriched beef to be equivalent to milk as a source of protein, Ca and P.

The cause for the occurrence of a slightly negative Ca balance in both boys during the milk feeding as well as the meat feeding period, despite a high Ca intake, is obscure. The Ca content of the previous diet did not differ greatly from that of the experimental diet. It was estimated to be approximately 1.5 gm. daily. There was a slight decrease in the daily motor activity when the patients were transferred from the general ward to the special metabolic ward. This may have had a decalcifying effect.[26] The vitamin D (1,000 u. daily) was assumed to be adequate. The feces were normal in amount and consistency. Johnston's[27] studies on Ca metabolism in essentially normal adolescent children disclosed an unusual tendency toward the development of a negative Ca balance which appears to be peculiar to the age period. This tendency, no matter what its underlying cause, may account for the small, negative Ca balances shown by the two subjects in the present study.

A few practical points regarding the use of the meat diet may be appropriate here. The texture and taste of finely divided cooked meat are such that the product can be served in a wide variety of ways to satisfy children of all ages, even after the essential salt mixture has been added. In preparing the meat for routine use as a milk substitute, it was found convenient to take 100 gm. of the cooked lean beef as a unit on which to base calculations. This furnishes the same amount of protein as 500 ml. or about one pint of whole milk. To it is added a unit quantity of a simple salt mixture, consisting of Ca-gluconate, 6.3 gm., dibasic K-phosphate (K_2HPO_4) 1.0 gm., and Mg-citrate 0.4 gm., to provide amounts of Ca, P, K, and Mg similar to those found in 500 ml. of cow's milk. The substitution of the dibasic K phosphate for the monobasic salt or phosphate mixture, used in most of our experiments, improved the taste of the product. The substitution results in a lowering of the P content of the diet to a level somewhat below that of cow's milk but still well above that of human milk. There are reasons to believe that this degree of reduction in P content is advantageous in infant nutrition.

For making a more nearly complete substitute for whole cow's milk, the mineral-enriched strained meat must have added to it butter fat, lard or a low-melting-point vegetable oil and carbohydrate in amounts similar to those in milk. For older children these, and even the essential minerals, may be obtained from the other items in their ordinary mixed diets. For bottle-fed infants, on the other hand, it is preferable to mix all ingredients of the diet together, adding sufficient water to equal that in fresh milk. Various degrees of sweetness of the formula can be obtained by appropriate selection of the carboydrates to be added.

To make a smooth, homogeneous formula in which the meat remains in fine suspension for as long a time as desired, one third to one half of the carbohydrate to be added is given in the form of thoroughly cooked rice gruel, the remainder being supplied as sucrose or other sugar. Thorough mixing is greatly facilitated by use of a mechanical mixer, such as the Waring Blender. A typical formula for use as a substitute for one pint of whole milk contains the following ingredients:

Strained beef	100.0 gm.
Salt mixture (Ca-gluconate 6.3 gm., K_2HPO_4 1.0 gm. and Mg-citrate 0.4 gm.)	7.7 gm.
Lard	16.5 gm.
Rice	16.0 gm.
Sucrose	12.8 gm.
Water	347.0 gm.
Total	500.0 gm.

This, like whole milk used in the ordinary infant's diet, should be supplemented with vitamins and added carbohydrates or other foods appropriate for the age. For the rare patient who manifests an allergic reaction to beef proteins, as well as to those of milk, other available meat products, such as lamb or pork, to which there may be no allergic reaction, should be substituted for the beef.

Summary

The nutritive value of cooked lean meat enriched with Ca, P and other minerals, as well as with fat, carbohydrate and vitamins, was compared with that of whole cow's milk in feeding experiments on young growing rats and on two adolescent boys. As judged by changes in body weight, whole carcass analyses, bone composition, blood serum analyses, character of the furry coat and spontaneous motor activity, growing rats thrived at least as well on the meat as on the milk regimen, when the two diets contained the same amounts of Ca, P, Mg and K, as well as protein, fat, carbohydrate and vitamins.

The meat formula without any mineral enrichment or with either Ca or P omitted from the salt mixture failed to support normal growth and normal bone composition in the rat.

Preliminary N, P and Ca balance studies on two adolescent human subjects showed the Ca- and P-enriched meat to be as good as or slightly better than milk as a source for these elements.

References

1. Kempster, E., and others, Utilization of calcium of dicalcium phosphate by children, J. Nutrition **20**:279, 1940.
2. Steggarda, F. R., and Mitchell, H. E., Calcium requirement of adult man and utilization of calcium in milk and in calcium gluconate, J. Nutrition **17**:253, 1939.

3. Holmes, J. O., in Wohl's Dietotherapy, Philadelphia, W. B. Saunders Company, 1945, chap. 8.
4. Fairbanks, B. W., and Mitchell, H. H., Availability of calcium in spinach, in skim milk powder and in calcium oxalate, J. Nutrition **16**:79, 1938.
5. Shields, J. B., Fairbanks, B. W., Berryman, G. H., and Mitchell, H. H., Utilization of calcium of carrots, lettuce and string beans in comparison with calcium in milk, J. Nutrition **20**:263, 1940.
6. Shroeder, L. J., Cahill, W. M., and Smith, A. H., Utilization of calcium in soybean products and other calcium sources, J. Nutrition **32**:413, 1946.
7. Krane, W., Mineralstoffwechsel bei kalkzufuhr, Arch. f. d. ges. Physiol. **24**:217, 1927.
8. Sherman, H. C., Chemistry of Food and Nutrition, ed. 7, New York, The Macmillan Company, 1945.
9. Orr, W. J., Holt, L. E., Jr., Wilkins, L., and Boone, F. H., Relation of calcium and phosphorus in diet to absorption of these elements from intestine, Am. J. Dis. Child. **28**:574, 1924.
10. Sollman, T., Manual of Pharmacology, Philadelphia, W. B. Saunders Company, 1943, p. 913.
11. Bergeim, O., Intestinal chemistry. V. Carbohydrate and calcium and phosphorus absorption, J. Biol. Chem. **70**:51, 1926.
12. Kline, O. L., Keenan, J. A., Elvehjem, C. A., and Hart, E. B., Lactose in nutrition, J. Biol. Chem. **98**:121, 1932.
13. Robinson, C. S., Huffman, C. F., and Mason, M. F., Results of ingestion of certain calcium salts of lactose, J. Biol. Chem. **84**:257, 1929.
14. Mitchell, H. H., Hamilton, T. S., and Beadles, J. R., Comparative nutritive values of glucose, fructose, sucrose and lactose when incorporated in complete diet, J. Nutrition **14**:435, 1937.
15. Mills, R., and others, Influence of lactose on calcium retention in children, J. Nutrition **20**:467, 1940.
16. McQuarrie, I., Ziegler, M. R., and Moore, I. H., Calcium-enriched meat compared with milk as source of calcium, phosphorus and protein, Proc. Soc. Exper. Biol. & Med. **65**:120, 1947.
17. Clark, E. P., and Collip, J. B., Study of Tisdall method for determination of blood serum calcium with suggested modification, J. Biol. Chem. **63**:461, 1925.
18. Kuttner, T., and Cohen, H. R., Micro colorimetric studies. I. Molybdic acid, stannous chloride reagent: Micro estimation of phosphate and calcium in pus, plasma and spinal fluid, J. Biol. Chem. **75**:517, 1927.
19. Howe, P. E., Determination of proteins in blood: Micro method, J. Biol. Chem. **49**:109, 1921.
20. Ma, T. S., and Zuazaza, G., Micro-Kjeldahl determination of nitrogen, Indust. & Engin. Chem. (Indust. Ed.) **14**:280, 1942.
21. Tisdall, F. F., and Kramer, B., Methods for direct quantitative determination of sodium, potassium, calcium, and magnesium in urine and stools, J. Biol. Chem. **48**:1, 1921.
22. Fiske, C. H., and Subbarow, Y., Colorimetric determination of phosphorus, J. Biol. Chem. **66**: 375, 1925.
23. Morgulis, S., Studies in chemical composition of bone ash, J. Biol. Chem. **93**:455, 1931.
24. Leitch, I., Determination of calcium requirements on man, Nutrition Abstr. & Rev. **6**:553, 1937.
25. Adams, J. M., Kimball, A. C., and Adams, F. H., Early immunization against pertussis, Am. J. Dis. Child. **74**:10, 1947.
26. Deitrick, J. E., Effect of immobilization on metabolic and physiological functions of normal men, Bull. New York Acad. Med. **24**:364, 1948.
27. Johnston, J. A., Factors influencing retention of nitrogen and calcium in period of growth, Am. J. Dis. Child. **67**:265, 1944.

SPANISH ABSTRACT

Comparación del Valor Nutritivo de Carne y Leche Enriquecidas de Minerales

El valor nutritivo de la carne magra cocida enriquecida con Ca, P y otros minerales, lo mismo que con gordura, hidrato de carbono y vitaminas, fué comparado con el de la leche de vaca en experimentos de alimentación en ratas jovenes creciendo y dos muchachos adolescentes. Como se juzgaron por cambios en el peso de cuerpo, los análisis de todo el esqueleto, la composición de

hueso, los análisis del suero de sangre, el caracter de la capa de piel y la actividad de motor espontanea, las ratas que crecían se desarrollaron por lo menos tan bien con el régimen de carne como el de leche, cuando las dos dietas contenían las mismas cantidades de Ca, P, Mg y K, lo mismo que proteina, grasa, hidrato de carbono y vitaminas.

La formula de carne sin ningún enriquecimiento de mineral o con Ca o P omitidas de la mezcla de sal dejaron de mantener el crecimiento normal y la composición de hueso normal en la rata.

Estudios preliminares de balance N, P y Ca en dos sujetos humanos adolescentes mostraron que la carne enriquecida de Ca y P- es tan buena como, si no un poco mejor, la leche como fuente de estos elementos.

University of Minnesota Medical School

TREATMENT OF MALARIA IN CHILDREN WITH CHLOROQUINE

By THOMAS L. NELSON, M.D., AND GERALD J. CONLIN, MAJOR, M.C., U.S.A.
Ancon, Canal Zone

THE use and advantages of chloroquine over older drugs in the treatment of malaria of adults has been well described by Loeb[1] and Most.[2] As pointed out by Einhorn,[3] the clinical manifestations and treatment of malaria in children may be considerably different from those in adults. Enriquez-Navarro[4] has reported on the treatment with chloroquine of 10 children, and Berberian and Dennis[5] reported on the treatment with chloroquine of adults and children in field experiments in two Lebanese villages. The purpose of this study was to evaluate better, under close hospital observation, the use of chloroquine for malaria in children.

METHOD

The chloroquine (SN 7618) used in this study was in the form of the diphosphate which is 7-chloro-4-(4-diethylamino-1-methyl butylamino) quinoline diphosphate. It is available in 0.25 gm. tablets which contain approximately 0.15 gm. of chloroquine base.

Fifty-four consecutive cases of malaria in children ranging in age from 8 mos. to 12 yrs., with an average age of 4.9 yrs., were treated with chloroquine diphosphate. Of these 54 cases, 32 were

TABLE I

DOSAGE SCHEDULE OF CHLOROQUINE DIPHOSPHATE BY AGE

Age	Total dose*	Dose on entry	Dose in 8 hrs.	Dose on each of following 2 days
6–18 mos.	0.60 gm.	1½ tab.	½ tab.	1 tab.
18 mos.–5 yrs.	0.75 gm.	2 tab.	1 tab.	1 tab.
5–8 yrs.	0.975 gm.	3 tab.	1½ tab.	1½ tab.
over 8 yrs.	1.50 gm.	4 tab.	2 tab.	2 tab.

One tablet of chloroquine diphosphate is 0.25 gm. and contains 0.15 gm. chloroquine base.
* Total dose is calculated by wt. of chloroquine base.

due to Plasmodium vivax, 21 were due to Plasmodium falciparum and 1 case was due to a mixed P. vivax and P. falciparum infection. Nine of the 54 cases were regarded as severe, having evidence of cerebral involvement or appearing unusually toxic.

All patients were hospitalized for at least 6 days and had examinations of thick and thin blood smears for malaria daily for the 1st 6 days after starting treatment. Temperatures were taken every 4 hrs. during fever and all patients were observed closely for toxic symptoms. Although all patients were requested to return to the outpatient department following hospitalization, only 33% (18 patients) returned at least once for physical examination and malaria smears; of these, only 4 were followed for 6 mos. or more. However, under the system of medicine practiced in the Canal Zone, most clinical relapses would be brought to the outpatient department; by Canal Zone Health Department policy, all persons with malaria are hospitalized.

The 1st 15 cases were treated with a total dose of chloroquine base 0.015 gm./lb. body wt., divided into 2/5 as initial dose, 1/5 in 8 hrs. and 1/5 on each of the 2nd and 3rd days. The other

From the Pediatric Section, Gorgas Hospital, Ancon, Canal Zone.
(Received for publication May 19, 1949.)

TABLE II

DETAILED TABLE OF RESULTS

Case No.	Type of malaria*	Age yrs.	Wt. in lbs.	No. of days of parasitemia†	Days of fever after starting therapy	Known recurrences, toxic symptoms and remarks
1	F	5	36	1	1	
2	V	5	42	3	2	Anorexia
3‡	F	16/12	29	3	1	
4	V	12	62	2	3	
5	V	7	54	3	2	
6	V	2	30	2	3	
7‡	V	5	42	2	3	Recurrence in 6 mos. #41
8	V	5	42	2	3	
9	V	16/12	24	3	2	
10	F	6	38	2	2	Recurrence in 2 mos. #28
11	V	2	23	3	2	Recurrence in 3 mos. #31
12‡	F	2	21	3	2	Anorexia and listlessness
13	V	2	25	2	1	Anorexia. Recurrence 6 mos. #46
14‡	F	10	56	3	4	
15	F	8	67	2	3	Vomiting
16	F	5	36	3	5	Gametocytes for 5 days
17	F	12	80	2	1	Gametocytes for 8 days
18‡	F	2	20	3	1	
19‡	F	12	94	1	1	Alleged recurrence 7 days
20	V	3	30	3	4	Recurrence in 16 days #21
21	V	3	30	2	1	
22	V	18/12	22	1	2	
23	V	9	63	1	2	Listlessness
24	V	7	45	1	1	
25	F	11/12	15	1	5	
26	F	7	37	1	1	Nausea, vomiting, vertigo
27	V	16/12	17	3	2	Anorexia and listlessness
28	V	6	39	1	2	
29	V	3	31	4	3	
30‡	F	18/12	23	3	3	Listlessness
31	V	3	24	3	0	Anorexia
32	F	11	74	1	2	
33	F	8	52	3	3	Anorexia
34	V	5	38	1	0	
35‡	V&F	8/12	19	2	4	Listlessness
36	V	6	42	2	2	Nausea and vomiting
37	V	5	32	2	1	
38	F	4	37	1	2	
39	V	5	38	3	2	
40	F	9	53	3	2	Listlessness
41	V	6	49	3	1	Nausea and vomiting
42	V	5	38	3	2	
43	V	2	29	2	1	Anorexia and listlessness
44	V	5	37	3	2	Anorexia and listlessness
45	V	4	35	2	2	Nausea and vomiting
46	V	2	28	2	1	Anorexia and listlessness
47	F	14/12	20	1	2	
48	F	11	56	1	1	
49	F	2	27	1	1	Gametocytes for 8 days
50	F	3	34	2	2	Listlessness; gametocytes 12 days
51	V	12/12	18	2	2	
52	V	7	58	2	2	
53‡	V	3	32	2	1	Nausea and vomiting
54	V	6	44	2	2	

* V—P. vivax malaria; F—P. falciparum malaria.
† This is no. of days of parasitemia exclusive of gametocytes of P. falciparum.
‡ Severely ill cases.

39 cases were treated by a schedule according to age (Table I). Any dose of medication vomited was immediately repeated. In all cases a 3 day treatment schedule was used.

Results

All patients rapidly became asymptomatic and by the fourth day all had negative blood smears except for five patients showing sexual forms of P. falciparum. The average number of days of parasitemia, excluding P. falciparum gametocytes, was 2.1. Maximum duration of fever was five days, average two days. There were no deaths.

Twenty patients complained of or exhibited listlessness, vertigo, nausea, vomiting or anorexia during treatment. Because malaria classically produces these manifestations, no attempt is made to represent them as evidence of chloroquine toxicity alone. Two children who persistently vomited their medication retained chloroquine introduced by gastric tube. However, of a control group of 16 nonmalarial (tuberculous) children given dosage according to Table I, 10 manifested vomiting and anorexia and one complained of vertigo and double vision. All retained medication after sedation.

Four malarial patients tested showed a positive cephalin-cholesterol flocculation reaction. Although this phenomenon is common in malaria, a possible relationship to chloroquine therapy was considered, and the 16 nonmalarial children were noted to have no change in icterus index, Van den Bergh reaction or cephalin-cholesterol flocculation reaction four days after starting the chloroquine therapy.

Six patients had more than one bout of symptomatic malaria. Patients 7, 11, 13 and 20 had recurrences of P. vivax malaria two weeks to six months after the first episode. Patient 10 had P. vivax malaria two months after leaving the hospital apparently cured of P. falciparum malaria. Patient 19, a 42.6 kg. boy violently ill with P. falciparum malaria, was treated for malaria by another physician seven days after cessation of our therapy, and is regarded by us as a possible treatment failure.

Four patients showed gametocytes of P. falciparum for variable periods (2 to 12 days) after the chloroquine treatment. A detailed table of results is included (see Table II).

Summary

Forty-nine children with 54 episodes of malaria were treated with chloroquine with four known relapses and one suspected treatment failure.

A dosage scale for children is offered (Table I).

Only minor toxic effects of chloroquine were observed.

Chloroquine did not prevent the presence of the gametocytes of Plasmodium falciparum in peripheral blood.

Nine cases severely ill with malaria responded well to this treatment.

Conclusion

Chloroquine in dosage given (Table I) is recommended as a rapid, safe and efficient therapy for malaria in children.

References

1. Loeb, R. F., and others, Activity of new antimalarial agent, chloroquine (SN 7618): Statement approved by board for coordination of malarial studies, J.A.M.A. **130**:1069, 1946.
2. Most, H., and others, Chloroquine for treatment of acute attacks of vivax malaria, J.A.M.A. **131**:963, 1946.

3. Einhorn, N. H., Tertian, quartan and mixed malarial infections: Survey of three hundred and thirty-four cases of infection with plasmodium vivax, ten cases of infection with plasmodium malariæ and eight cases of mixed malarial infections in children, Am. J. Dis. Child. **73**:55, 1947.
4. Enriquez-Navarro, A. F., and Rognoni, M., Uso del Aralen (Chloroquina Winthrop) en el Tratamiento de la Malaria Aguda en niños, Arch. Hosp. Santo Tomás **3**:35, 1948.
5. Berberian, D. A., and Dennis, E. W., Field experiments with chloroquine diphosphate, Am. J. Trop. Med. **28**:755, 1948.

SPANISH ABSTRACT

Tratamiento de Malaria en Niños con la Cloroquina

Se trataron 49 niños con 54 episodios de malaria con cloroquina bajo cerca observación del hospital. De estos 54 casos, 32 fueron debidos a P. vivax, 21 fueron debidos a P. falciparum y 1 caso fué debido a una infección mezclada de P. vivax y P. falciparum. Nueve casos severamente enfermos con malaria respondieron bien a este tratamiento. Solamente se observaron menores efectos tóxicos. La cloroquina en dosis dadas se recomienda como una terapia rápida, segura y eficaz para malaria en los niños.

901 Grizzly Peak Boulevard, Berkeley, Calif.

ETIOLOGIC FACTORS IN TETANY OF NEWLY BORN INFANTS

By LYTT I. GARDNER, M.D.,* ELSIE A. MACLACHLAN, B.S., WALTER PICK, M.D., MARY L. TERRY, B.A., AND ALLAN M. BUTLER, M.D.
Boston

PINCUS and Gittleman[1] presented evidence that nonrachitic tetany in a 7 weeks' old infant was associated with a transient hypoparathyroidism. Bakwin[2] suggested the etiology of tetany of the newborn infant to be the high phosphorus intake of cow's milk together with such a hypoparathyroidism. He pointed out that this syndrome is virtually unknown where breast feeding of newborn infants is the custom and that newborn infants given phosphate solution by mouth showed a rise in serum inorganic phosphorus and fall in serum calcium concentrations such as is characteristic of neonatal tetany. Moreover,

TABLE I

DATA SHOWING DIETARY Ca:P RATIO AND CONCENTRATION OF P IN HUMAN MILK AND IN FORMULAS USED IN 16 CASES OF NEONATAL TETANY

Product	Ca:P Ratio	P mg./100 ml.	No. Cases Neonatal Tetany
Human milk	2.26	8–15	0
Cow's milk	1.27	50	2
Evaporated milk formula	1.05–1.27	50–55	5
Cow's milk product "I"	1.05	60	3
Cow's milk product "II"	1.00	53–98*	6
Total			16

* Concentration range for product "II" depends on accuracy used in measuring tablespoons of a powder.

the increase in neuromuscular irritability which may result in older infants and children from a low dietary Ca:P ratio[3–6] might be exaggerated by the limited ability of the newborn infant's kidneys to excrete P, as suggested by Dean and McCance.[7] Their studies, however, were conducted largely on breast-fed infants thus leaving some doubt as to whether the low P clearance was the result entirely of a specific limitation in renal function or partially of a physiologic hypoparathyroidism to conserve needed P.

This paper reports certain clinical and metabolic observations which appear to provide additional evidence concerning the three etiologic factors mentioned above: dietary intake of Ca and P, parathyroid function and renal function.

From the Children's Medical Service, Massachusetts General Hospital, and The Department of Pediatrics, Harvard Medical School, Boston, Mass.

Supported in part by a research grant from the Division of Research Grants and Fellowships of the National Institutes of Health and the National Heart Institute, U.S. Public Health Service, Federal Security Agency.

Received for publication April 20, 1949.

* Research Fellow in Pediatrics, Harvard Medical School.

TABLE II

CA AND P CONTENT OF COW'S MILK AND OF HUMAN MILK IN NEONATAL PERIOD

Patient	Day of Lactation	Ca mg./100 ml.	P mg./100 ml.	Ca:P Ratio
1	1	20.4	8.4	2.43
1	3	23.7	10.5	2.26
1	5	16.8	8.7	1.93
2	1	14.0	7.3	1.92
3	4	23.6	8.7	2.69
	Mean Values =	19.7	8.7	2.26
Cow's milk (fresh, skimmed, undiluted)		122.0	96.0	1.27
Cow's milk product "I" (evaporated, undiluted)		230.0	219.0	1.05
Cow's milk product "II" (spray dried, diluted)		52.0*	53.0*	1.00
		104.0†	106.0†	

* Normal dilution (1 tablespoon powder/2 fluid oz. water).

† Dilution recommended by manufacturer for premature infants and full term infants "unable to tolerate a normal amount of fluid" (1 tablespoon powder/1 fluid oz. water).

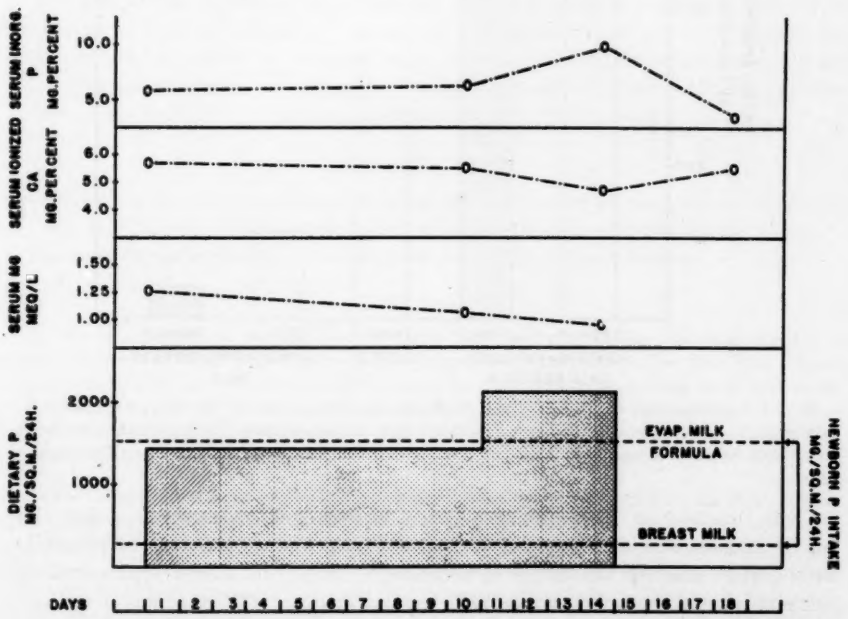

CHART 1. Data of Salvesen, Hastings and McIntosh[8] on 15 kg. dog given neutral HPO_4 by stomach tube. Upper portion of chart shows effect of HPO_4 on serum concentrations of inorganic P, Ca and Mg in dog. Lower portion compares P intake/sq. m. surface area/24 hrs. of dog (shaded area) with that of cow's milk-fed newborn infant (upper dotted line) and human milk-fed newborn infant (lower dotted line).

Comparison of Cow's Milk and Breast Milk

A review of 16 cases of neonatal tetany seen at the Massachusetts General Hospital in the last two years reveals that all were fed with cow's milk. Table I gives the Ca:P ratios and total P-content of the various milk preparations this group of newborn infants received. It is noteworthy that commercial preparation "II," which was used in a large number of cases, has the lowest Ca:P ratio and highest P content of any preparation this group received.

Table II shows Ca and P analyses done in this laboratory on human milk in the neonatal period compared with cow's milk and two commercial cow's milk preparations for infants. The table shows marked differences in Ca and P concentration and Ca:P ratio between human milk and the various preparations of cow's milk.

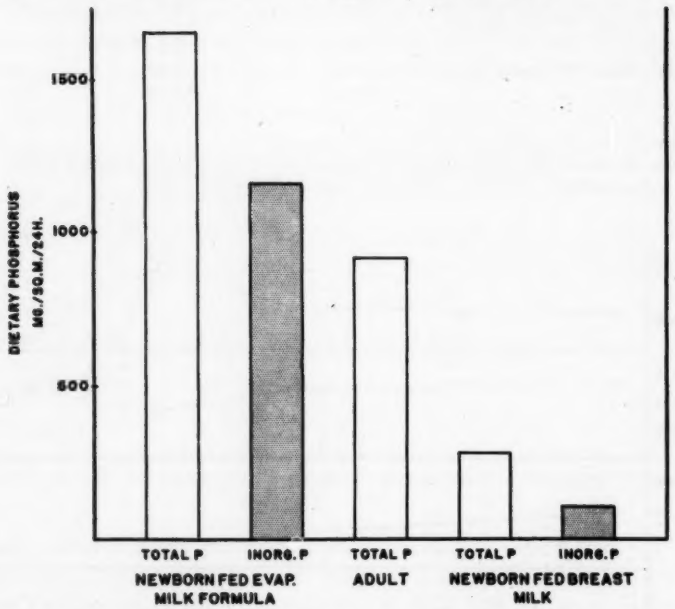

Chart 2. Comparison of daily P intake as mg./sq. m. surface area of newborn infant fed cow's milk formula, adult on average diet, and newborn infant fed human milk. Shaded columns emphasize discrepancy between inorganic P intake of cow's milk-fed newborn infant and breast-fed newborn infant.

Chart 1 outlines an experiment of Salvesen, Hastings and McIntosh[8] on a dog when fed by stomach tube daily amounts of neutral HPO_4 which greatly exceed per square meter surface area the amount given a breast-fed infant, but closely approximate the intake of many formula-fed infants. With the ingestion of HPO_4 there was elevation of serum inorganic P and reduction of Mg and ionized Ca. Improvement occurred when HPO_4 was withdrawn. Chart 2 compares the daily P intake per square meter surface area of a cow's milk-fed newborn infant with the daily P intake of an adult and a breast-fed newborn infant.* The figure shows that the cow's milk-fed newborn infant may ingest

* Figures for phosphorus intake are from feeding data in the newborn nursery of this hospital. The adult value was calculated from Sherman's data.[11]

more inorganic P per square meter per day than the total P intake per square meter per day of the average adult. There is relatively more inorganic P in cow's milk (70% of total P) than in human milk (36% of total P).[9,10] Cow's milk contains less Ca and much less Mg relative to P than does breast milk.[11]

In addition to the low Ca:P ratio, cow's milk has a much higher buffer value than human milk.[12] Five times as much HCl is required to cause a given amount of cow's milk to dialyze its maximum amount of Ca in vitro as is required to cause the same result in a given volume of breast milk.[13,14] That cow's milk produces an enteric alkalosis is suggested by the observation that infants fed undiluted cow's milk had stool pH's averaging 7.4, whereas those fed breast milk averaged 4.9.[15] This increase of pH in the gut may inhibit Ca absorption since the free absorption of Ca is limited to a small portion of the upper gut while still in acid solution.[16,17]

Relation of Cow's Milk Feeding to Parathyroid Histology

A review of the autopsy protocols and clinical records of a number of the infants whose parathyroid histology was studied by Kaplan[18] in the neonatal period revealed reliable dietary histories for 15 infants.* The parathyroids of eight newborn infants fed cow's milk were classified "idiopathic hypertrophy." The glands of seven breast-fed newborn infants were classified as "normal" parathyroids (aged 4 hours to 28 days).

The parathyroid volume of rats (measured from serial sections) increases with a low dietary Ca:P ratio and decreases with a high Ca:P ratio.[19] Parathyroid hyperplasia has been produced in rabbits by the intravenous injection of HPO_4.[20] Hence it would seem likely that the "idiopathic" hypertrophy of the parathyroid in the cow's milk-fed newborn infant is associated with the relative and absolute excess of P in the diet.

Metabolic Data

Although serum concentrations were followed in only seven patients, renal P clearances in two, and balance studies completed on only one, the data obtained appear of significance concerning the etiology, prevention and treatment of neonatal tetany.

Methods

In the first portion of the experiment, healthy male newborn infants, with body weights as similar as possible, were used. They were all vigorous eaters and had similar daily fluid intakes. The cow's milk-fed subjects received the routine evaporated milk formulas that were used in the newborn nursery of this hospital.† Both bottle- and breast-fed infants observed the same time schedule for feeding. The breast-fed infants were weighed before and after each feeding to determine their intake.

* The authors are indebted to Dr. Sidney Farber, Pathology Dept., Children's Hospital, Boston, Mass., who made available the autopsy protocols.

† Beginning on the 2nd day of life and continuing to about the 6th day, formula "A" is used. Except for the 2nd day of life when 2 feedings are given, 6 feedings of approximately 70 ml. each are given daily. Later formula "B" is used. Six feedings are given daily of 90 ml. each. Each bottle-fed newborn received ascorbic acid 50 mg. and vitamin D_3 750 u. per day by mouth. The breast-fed newborns received no added vitamins.

Formula	Evap. Milk ml.	Water ml.	Cane Syrup ml.	P mg./ 100 ml.	Ca mg./ 100 ml.	Cal./ 100 ml.
"A"	100	300	20	52.2	54.7	55
"B"	150	350	40	61.7	64.6	66

Capillary blood was collected for serum inorganic P just before the 6 p.m. feeding. All other determinations were done on venous blood. Toluene was added as a preservative to the 24 hr. urine collections on infant T.M.

The analytic procedures employed are as follows: (a) Ca, method of Fiske and Logan[23]; (b) P, method of Fiske and Subbarow[22]; (c) Mg, a modification of Briggs' method[25]; (d) N, determined by the Kjeldahl method using a boric acid mixed indicator.

I. Observations on serum inorganic phosphorus, serum ionized calcium and total phosphorus intake in the neonatal period.

Chart 3 gives observations on the daily serum inorganic P levels and total P intake of two breast- and four cow's milk-fed infants during the newborn period. In the upper portion of the chart serum inorganic P in mg./100 ml. is plotted against day of life as the abscissa. Breast-fed subjects are represented by dotted lines and cow's milk-fed infants by a continuous line. In the lower half of the chart total P intake in mg./sq. m. surface area is plotted against day of life. The chart shows that after the first three days of life the cow's milk-fed subjects had higher inorganic P values than the breast-fed subjects.

Table III compares the P intakes with serum concentrations in two breast- and two formula-fed infants on whom serum Ca as well as inorganic P analyses were done. The values for ionized Ca were calculated from the serum total Ca concentration and serum total protein by means of the McLean-Hastings nomogram.[24]

Chart 3 and Table III show that values of serum inorganic P and ionized Ca ordinarily associated with the syndrome of neonatal tetany may occur in newborn infants fed cow's milk without clinical evidence of tetany.

Bakwin[2] gave inorganic P 350-625 mg./sq. m. to newborns in one feeding and produced

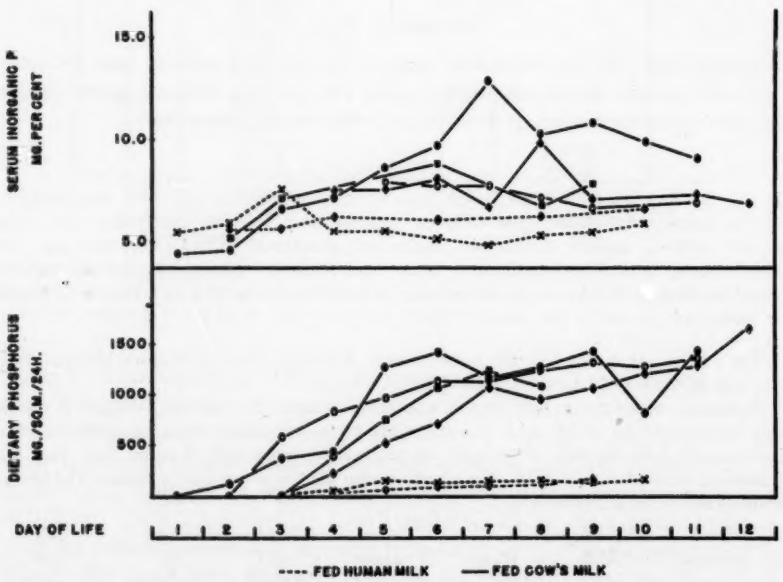

CHART 3. Comparison of daily serum inorganic P concentrations and P intakes of 4 newborn infants fed cow's milk formulas (solid lines) and 2 newborn infants fed human milk (dash lines).

TABLE III

DATA SHOWING RELATION OF DIET TO P INTAKE FROM 3RD TO 10TH DAY OF LIFE AND DETERMINED CONCENTRATIONS OF SERUM P, CA AND BLOOD NPN TOGETHER WITH CALCULATED CA-ION CONCENTRATIONS FOR INFANTS ON HUMAN OR COW'S MILK REGIMES

Infant	Diet	Ave. P Intake mg./sq.m./day	Serum P (max.)		Total Ca mg./100 ml.	TP gm./100 ml.	Ca^{++} mg./100 ml.	NPN mg./100 ml.	Day of life
			mg./100 ml.	Day of life					
BG	Breast	205	7.6	3	8.6	5.5	4.3	20	8
LG	Breast	190	6.9	10	8.8	5.5	4.5	19	7
BK	Bottle	1,020	12.9	7	6.2	5.7	3.0	30	8
TM	Bottle	981	10.3	8	6.1	5.4	2.9	28	12

serum inorganic P levels as high as 18 mg./100 ml. There were no clinical signs of tetany or changes in the Chvostek reaction.[25]

II. Observations on the effect of variation in the dietary Ca:P ratio on phosphorus, calcium, magnesium and nitrogen metabolism in a full term newborn infant.

Ca, P and Mg balance data obtained on infant T.M. from the 4th through the 24th day of life are shown in Table IV. For the first 12 days the infant ingested the routine formulas as described. On the 13th day enough Ca lactate was added to the formula to make its Ca:P ratio exceed that of breast milk.

The data show that the infant began excreting relatively large quantities of urinary P soon after receiving the cow's milk formula. Coincident with this was a rise in serum inorganic P to high levels (Day 8, Period II) and a fall in serum ionized Ca and total Mg to low levels (Day 12, Period III). No clinical symptoms of tetany were observed. An increase in the Ca intake in Period IV was associated with a diminution of the serum inorganic P levels to values similar to those of the breast-fed newborn (see Chart 3) and with return of the serum ionized Ca and total Mg to normal levels. During Period IV there was marked increase in fecal P, less retention of P and decrease of urinary P toward the amounts excreted daily by breast-fed infants (0 to 20 mg., cf. Table V).[26, 27] There was also increased Ca retention, and diminished Mg and N retention.

If absorption is defined as dietary intake minus fecal excretion, it may be seen that Ca absorption from the gut in Period IV increased 4-fold while urinary Ca remained slight. Coincidentally there was a fall in serum inorganic P-concentration, $\frac{\text{urine P}}{\text{absorbed P}}$ ratio, and total excretion, indicating diminution of excess absorbed P and increased deposition of P in bone or tissue. During this period serum total Mg rose to normal, while fecal Mg increased and therefore total absorption was decreased. This seemingly paradoxic action of Mg appears due to the decreased absorption of P plus increased absorption of Ca. Apparently large amounts of absorbed Ca pre-empt the available P in the deposition of $CaPO_4$ in bone. Such a deposition would be consistent not only with the rise in serum Mg but also its increased urinary excretion. The increase in urinary N in spite of the diminished absorption would also appear to reflect a decrease in the P available for deposition with N in tissue.

TABLE IV

METABOLIC DATA ON INFANT T.M. 12 MAY TO 1 JUNE 1948

Period	Intake	Urine	Feces	Balance	Urinary % of Intake	Fecal % Intake	Balance % Intake	Days of Life in Period	Serum				Dietary Ca:P Ratio
									Day of Life Det'nd	Serum Value	Serum Total Protein	Serum Ionized Ca	
Ca (mEq./24 hrs.)													
										mg./100 ml.	gm./100 ml.	mg./100 ml.	
I	14.15	.033	2.27	11.8	.233	16.0	84.5	5– 7	5	8.18	5.4	4.25	1.05
II	20.46	.119	3.90	16.4	.600	19.0	80.5	8–10	—	—	—	—	1.05
III	23.45	.107	4.88	18.4	.455	20.8	78.7	11–12	12	6.1	5.7	2.90	1.05
IV	90.40	.226	14.25	75.9	.250	15.8	84.0	13–20	17	9.9	6.0	4.8	4.80
V	24.12	.071	5.27	18.7	.294	21.9	77.5	21–22	22	8.2	5.9	3.9	1.05
VI	20.8	.063	6.55	14.1	.303	31.5	67.6	23–24	24	8.9	5.7	4.4	1.05
P (mg./24 hrs.)													
										mg./100 ml.			
I	238	49.8	13.3	175	19.9	5.4	73.5	5– 7	6	7.92			1.05
II	332	70.7	21.8	239	22.2	6.5	72.0	8–10	8	10.3			1.05
III	447	114.2	32.6	300	25.1	7.1	67.3	11–12	11	7.18			1.05
IV	364	51.1	135.3	178	14.2	36.2	49.0	13–20	18	6.57			4.80
V	412	129.4	43.1	239	27.1	9.1	58.2	21–22	22	5.89			1.05
VI	398	111.4	76.7	210	28.2	18.8	52.5	23–24	24	6.38			1.05
Mg (mEq./24 hrs.)													
										mEq./l.			
I	1.42	.113	.20	1.1	7.95	14.1	78.2	5– 7	5	1.56			1.05
II	1.98	.113	.63	1.2	5.70	31.8	62.4	8–10	—	—	—	—	1.05
III	2.71	.014	.75	1.9	0.54	27.6	71.6	11–12	12	0.34			1.05
IV	2.22	.025	1.17	1.0	1.12	52.7	46.1	13–20	17	1.40			4.80
V	2.43	.001	0.48	1.9	0.04	19.7	80.0	21–22	22	1.15			1.05
VI	2.42	.003	0.75	1.6	0.14	31.0	69.0	23–24	24	1.89			1.05
N (gm./24 hrs.)													
I	1.46	.305	.036	1.11	20.9	2.5	78.8	5– 7					1.05
II	2.04	.394	.067	1.57	19.3	3.3	79.6	8–10					1.05
III	2.78	.561	.072	2.15	20.1	2.6	79.4	11–12					1.05
IV	2.28	.738	.159	1.38	32.8	6.9	62.3	13–20					4.80
V	2.88	.791	.075	2.01	27.4	2.6	71.8	21–22					1.05
IV	2.49	.628	.082	1.77	25.2	3.2	73.4	23–24					1.05

When the added Ca lactate was omitted from the formula (Periods V and VI), serum ionized Ca and total Mg fell (although not so markedly as before) and then rose. The serum inorganic P did not change significantly. There was marked decrease in fecal P, increase in urinary P, increased over-all P retention, and restitution of Ca, Mg and N balances to foreperiod levels.

III. Observations on renal phosphorus clearances.

Chart 4 gives observations concerning renal P clearance of the full term newborn, T.M.,

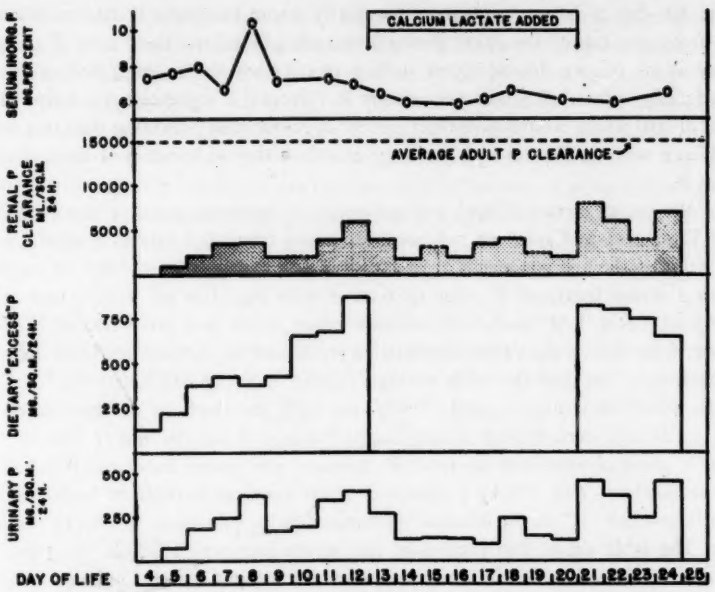

CHART 4. Observations on renal P clearance in full term newborn infant (T.M.) fed cow's milk formula from 5th to 25th day of life with Ca-lactate added days 13 to 20. Upper half of figure plots serum inorganic P as mg./100 ml. (at top) and daily renal P clearance as ml./sq. m. surface area/24 hrs. (shaded area). Horizontal dotted line indicates average adult P clearance as reported by Dean and McCance.[7] Lower half of figure shows dietary "excess" P and urinary P excretion as mg./sq. m. surface area/24 hrs.

TABLE V

CLEARANCE DATA ON INFANT J.M. 27 JAN. TO 21 FEB. 1949—PERIOD=24 HRS.

Period	Day of Life	Diet	Diet P mg./100 ml.	Serum P mg./100 ml.	Urine P mg./100 ml.	Urine P mg./24 hrs.	Urine Vol. ml./24 hrs.	P Clearance ml./sq. m. 24 hrs.
I	7	Human Milk	9	7.25	15.2	6.23	41	439
II	8	Human Milk	9	6.45	8.4	4.28	51	338
III	9	Cow's Milk Prod. II	106	11.26	80.8	25.05	31	1,136
IV	10	Cow's Milk Prod. II	106	11.26	396.0	31.68	8	1,421
V	11	Cow's Milk Prod. II	106	9.12	254.0	121.92	48	6,660
VI	17	Human Milk	9	6.56	17.6	15.50	88	1,205
VII	18	Human Milk	9	6.56	6.5	7.78	118	606
VIII	21	Human Milk	9	6.44	1.6	2.42	151	191

from the 4th day of life through the 24th. Daily serum inorganic P determinations are plotted across the top of the chart. Beneath this are plotted the daily renal P clearances expressed as ml. plasma cleared/sq. m. surface area/24 hrs. In the lower half of the chart is plotted daily "excess" P intake and urinary P. "Excess" P represents the daily P intake in excess of that which would have been present in breast milk providing the same amount of Ca. Hence with Ca:P ratio equal to or greater than that of breast milk there would be no excess P.

When the excess dietary P load was not great, P clearances were obtained similar to those of Dean and McCance[7] on newborns. In seven breast-fed infants studied by these authors[28] during the first two weeks of life the P clearance was 1600 ± 348* ml./sq.m./24 hrs. with a serum inorganic P value of 6.01 ± 0.59 mg./100 ml. Under high dietary excess P load infant T.M. reached P clearance values in the first two weeks of life which were more than double the values obtained on the breast-fed infants described above, but still considerably less than the adult average (dotted line, top half Chart 4). On Day 8, Period II, when the serum inorganic P was very high, the clearance did not exceed 3580 ml./sq. m./24 hrs. even though dietary excess P was 377 mg./sq. m./24 hrs.

Table V gives observations on renal P clearance and serum inorganic P values of a premature newborn (wt. 2.0 kg.) who was given alternate periods of breast milk and cow's milk product "II" in the dilution recommended for premature infants by the manufacturer. The table shows that the infant had serum inorganic P levels when on breast milk similar to the values for full term breast-fed infants in Chart 1. On breast milk total urinary P excretion was very low (4 to 5 mg./24 hrs.) and renal P clearances (300-400 ml./sq. m./24 hrs.) were somewhat lower than those of Dean and McCance in full term breast-fed infants. When this premature infant was changed from human milk to cow's milk product "II" (Period III), within 24 hours there was a rise of serum inorganic P to high levels (11.2 mg./100 ml.) with a 5-fold increase of urinary P. During Periods III and IV renal P clearance rose to only 1100 to 1400 ml./sq. m./24 hrs. in spite of the high serum inorganic P values. In Period V, still cow's milk product "II," urine volume and urine P excretion increased, and there was diminution of serum concentration of inorganic P. This may represent, as previously suggested, compensatory hyperplasia of parathyroid tissue. The infant was again given breast milk in Periods VI, VII and VIII. This was associated with a fall both in serum inorganic P and urinary P excretion.

Comment

Reported studies[29] on newborn infants indicate glomerular filtration rates of approximately 40,000 ml./sq. m./24 hrs. as compared to 100,000 ml. for the adult. The maximum P clearance of 3,580 ml./sq. m./24 hrs. observed in our studies thus approximates but 10% of the probable glomerular filtration rate. This is in marked contrast to the adult whose P clearance may be 50% of the glomerular filtration rate.[30] This difference appears to reflect parathyroid function.[30]

Prenatal factors may depress embryonic parathyroid function, since maternal hyperparathyroidism[31, 32] has been associated with hypocalcemia in the offspring. It has been shown that when the dietary Ca:P ratio of pregnant rats was increased, parathyroid size of embryos decreased.[33] Whether prenatal factors play a role in the etiology of neonatal tetany or not, the foregoing clinical observations and experimental data suggest that in

* Mean ± standard deviation.

the newborn infant limitation in kidney function per se and physiologic hypoparathyroidism result in a limitation in the renal excretion of P. That the newborn infant's kidneys can respond to parathyroid hormone is evidenced by the increased urinary excretion of P observed in recent studies[30] following the injection of parathyroid hormone in infants. In the presence of such limitations the Ca and P content of cow's milk predisposes infants fed cow's milk formulas* in the neonatal period to tetany. Park[34] has observed that the rise in serum P and fall in serum Ca which follows the ingestion of a high P diet by young rats does not occur if the diet had been supplemented with vitamin D. Bakwin,[2] however, found no such effect of vitamin D in the newborn infant receiving a high P intake.

TABLE VI

MODIFICATION OF COW'S MILK TO PRODUCE FORMULA SUITABLE FOR NEONATAL PERIOD

	Cow's Milk (undiluted) A	Cow's Milk (dil. 1:2) B	Additions to B	Cow's Milk Neonatal Formula C	Human Milk D
Protein gm./100 ml.	3.5	1.17	—	1.17	1.5
Carbohydrate gm./100 ml.	4.5	1.5	8.5	10.0	7.5
Fat gm./100 ml.	4.0	1.33		1.33	4.0
Cal./100 ml.	66	22	35	57	66
Ca mg./100 ml.	120	40	25*	65	20
P mg./100 ml.	90	30	—	30	9
Ca:P ratio	1.3	1.3		2.2	2.2

* Added as U.S.P. Ca-gluconate (0.28 gm./100 ml. formula). Vitamins A, D and C to be added.

The low P content and relatively high Ca:P ratio of breast milk make it, as might be expected, a highly physiologic diet for the newborn infant. If breast milk is unavailable, one third strength cow's milk with supplementary carbohydrate, Ca and vitamins A, D and C is suggested for the first two weeks of life as shown in Table VI. From such data as are available it appears that dilution of one part of milk with two parts of water without the addition of Ca may be found satisfactory in preventing hyperphosphatemia in the neonatal period.

SUMMARY AND CONCLUSIONS

Sixteen cases of neonatal tetany are reported, all of whom were fed cow's milk formulas.

Relative to human milk, cow's milk has a low Ca:P ratio and increased total P concentration. These differences are accentuated in some commercial milks prepared for infant feeding.

Cow's milk, even if diluted 2:1 with water, is an unphysiologic food for the human infant in the neonatal period, producing elevated serum P and decreased serum Ca and Mg levels.

* It may be noted that the manufacturer may legally add disodium phosphate (0.1% by wt.) in the processing of evaporated milk.[35] This further reduces the Ca:P ratio of the milk. Cow's milk product "II," previously mentioned, is treated by a patented process which involves the addition of phosphoric acid and consequently has a Ca:P ratio of 1.0, the lowest encountered by the authors.

Increasing the Ca:P ratio of cow's milk to that of human milk or dilution 1:2 with water limits the abnormal changes in serum P, Ca and Mg concentrations referred to.

A high P diet of an inadequately diluted cow's milk formula causes hypertrophy of the parathyroid glands of the newborn infant.

The maximum renal P clearance of the human newborn infant in the first week of life appears to approximate 3500 ml./sq. m./24 hrs.

Our observations indicate that when newborn infants are fed cow's milk formulas commonly used in this country limitation in parathyroid and renal function predisposes to tetany.

The foregoing data emphasize the physiologic character of human milk for the newborn infant. If breast milk is unavailable, a suitable formula for the neonatal period appears to be cow's milk 1 part, water 2 parts, 10% carbohydrate and Ca-gluconate to produce a Ca:P ration approaching that of breast milk. The added water and Ca should then be gradually reduced.

ACKNOWLEDGMENT

The authors wish to express their appreciation to Mrs. Anna Peterson, Miss Margaret McHugh and Mrs. Mary Curtis of the Massachusetts General Hospital nursing staff, whose assistance made these studies possible.

REFERENCES

1. Pincus, J. B., and Gittleman, J. F., Infantile tetany: Metabolic study, Am. J. Dis. Child. **51**:816, 1936.
2. Bakwin, H., Tetany in newborn infants, Am. J. Dis. Child. **54**:1211, 1937.
3. Finkelstein, H., Zur Kenntniss der Tetanie und der tetanoiden Zustände der Kinder, Fortschr. d. Med. **20**:665, 1902.
4. Jeppsson, K., and Klercker, G. O., Untersuchungen über die Bedeutung der Alkaliphosphate für Spasmophilie, Ztschr. f. Kinderh. **28**:71, 1921.
5. Klercker, G. O., and Oden, M., Zur Frage der Genese der sog. Phosphat-tetanie, Acta paediat. **5**:79, 1925.
6. Dodd, Katherine, Buddingh, G. J., and Rapoport, S., Etiology of Ekiri: Highly fatal disease of Japanese children, PEDIATRICS **3**:9, 1949.
7. Dean, R. F. A., and McCance, R. A., Phosphate clearances in infants and adults, J. Physiol. **107**:182, 1948.
8. Salvesen, H. A., Hastings, A. B., and McIntosh, J. F., Blood changes and clinical symptoms following oral administration of phosphates, J. Biol. Chem. **60**:311, 1924.
9. Lenstrup, E., Phosphorus content of human milk and cow's milk, J. Biol. Chem. **70**:193, 1926.
10. Hess, A. F., and Benjamin, H. R., Comparative analysis of forms of calcium and inorganic phosphorus in human and cow's milk, Proc. Soc. Exper. Biol. & Med. **30**:1358, 1933.
11. Shohl, A. T., Mineral Metabolism, ed. 1, New York, Reinhold Publishing Corporation, 1939, p. 73.
12. Cox, W. M., and Mueller, A. J., Composition of milk from stock rats and apparatus for milking small laboratory animals, J. Nutrition **13**:249, 1937.
13. Zotterman, Yngve, Studies on calcium dialysis from cow milk and human milk, Acta paediat. **5**:180, 1925.
14. Marriot, W. McK., Davidson, L. T., and Harshman, L. T., Studies on digestion in infancy: Hydrogen ion concentration of gastric contents, Tr. Am. Pediat. Soc. **34**:39, 1922.
15. Gerstly, Jesse R., Cohn, D. J., and Lawrence, Grace, Rickets: Study of calcium and phosphorus metabolism and of clinical findings as influenced by certain feedings, J. Pediat. **27**:521, 1945.

16. Telfer, S. V., Calcium and phosphorus metabolism: Excretion of calcium and phosphorus, Quart. J. Med. **16**:45, 1922.
17. Telfer, S. V., Absorption of calcium and phosphorus and their fixation in skeleton, Quart. J. Med. **17**:245, 1924.
18. Kaplan, E., Parathyroid gland in infancy, Arch. Path. **34**:1042, 1942.
19. Stoerk, H. C., and Carnes, W. C., Relation of dietary calcium-phosphorus ratio to serum calcium and parathyroid volume, J. Nutrition **29**:43, 1945.
20. Drake, T. G., Albright, F., and Castleman, B., Parathyroid hyperplasia in rabbits produced by parenteral phosphate administration, J. Clin. Investigation **16**:203, 1937.
21. Fiske, C. H., and Logan, M. A., Determination of calcium by alkalimetric titration, J. Biol. Chem. **93**:211, 1931.
22. Fiske, C. H., and Subbarow, Y., Colorimetric determination of phosphorus, J. Biol. Chem. **66**:375, 1925.
23. Briggs, A. P., Determination of magnesium, J. Biol. Chem. **59**:255, 1924.
24. McLean, F. C., and Hastings, A. B., State of calcium in fluids of body, J. Biol. Chem. **108**:285, 1935.
25. Bakwin, H., Personal communication to the authors.
26. Birk, W., Beitrage zur Physiologie des Neugeborenen Kindes. Die bedeutung des Kolostrums. Analysen und Stoffwechselversuche, Monatschr. f. Kinderh. **9**:595, 1910.
27. Benjamin, H. R., Gordon, H. H., and Marples, E., Calcium and phosphorus requirements of premature infants, Am. J. Dis. Child. **65**:412, 1943.
28. Dean, R. F. A., Personal communication to the authors.
29. Dean, R. F. A., and McCance, R. A., Inulin, diodone, creatinine and urea clearances in newborn infants, J. Physiol. **106**:431, 1947.
30. Crawford, J. D., Osborne, M. M., Jr., Talbot, N. B., and Terry, M. L., Parathyroid glands and phosphorus homeostasis, to be published.
31. Friderichsen, C., Hypocalcämie bie einem Brustkind und Hypercalcämie bei der Mutter, Monatschr. f. Kinderh. **75**:146, 1938.
32. Schwartzer, K., Über die Blutkalkregulation beim Neugeborenen, Klin. Wchnschr. **19**:107, 1940.
33. Sinclair, J. G., Fetal rat parathyroids as affected by changes in maternal serum calcium and phosphorus through parathyroidectomy and dietary control, J. Nutrition **23**:141, 1942.
34. Park, E. A., Personal communication to the authors.
35. Evaporated Milk: Identity, Federal Register, July 2, 1940, p. 2444.

SPANISH ABSTRACT

Factores Etiológicos en Tetania del Recién-Nacido

Se reportan dieciseis casas de tetania neonatal, habiendo sido todos aliementados con formulas de leche de vaca.

Con relación a la leche humana, la lecha de vaca tiene una proporción baja de Ca:P y una concentración P total aumentada. Estas diferencias están acentuadas en algunas leches comerciales preparadas para la alimentación de infantes.

La leche de vaca, aún diluída 2:1 con agua, no es un alimento fisiológico para el infante humano en el período neonatal, produciendo suero P elevado y suero Ca disminuído y cantidades Mg.

Aumentando la proporción Ca:P de la leche de la vaca al de la leche humana o dilución 1:2 con agua limita los cambios anormales en el suero P-, Ca y concentraciones Mg de que hablamos arriba.

La dieta-P alta de una formula de leche de vaca inadecuadamente diluída causa hipertrofia de las glándulas paratiroides del infante recién-nacido.

La salida-P renal máxima del recién nadido en la primera semana de vida ser aproximada a 3500 ml./sq. m./24 horas.

Nuestras observaciones indican que cuando los infantes recién nacidos son alimentados con formulas de leche de vaca comunmente usadas en este país, la limitación en paratiroides y función renal tienen predisposición a tetania.

El informe de arriba da énfasis al carácter fisiológico de la leche humana para el infante recién-nacido. No si hay leche de pecho, una formula adecuada para el período neonatal parece ser 1 parte leche de vaca, 2 partes de agua, 10% hidrato de carbono y gluconato Ca para producir una proporción Ca:P que se acerque a la proporción de la cheche de pecho. El agua agregada y Ca deben entonces ser gradualmente reducidas.

Massachusetts General Hospital

PALMAR DERMATOGLYPHICS IN MONGOLISM

By HAROLD CUMMINS, PH.D., CAROLYNN TALLEY, M.D.,
AND R. V. PLATOU, M.D.
New Orleans

PHYSICAL expressions of the syndrome of mongolism are variable, and little information is available concerning the relative frequency and diagnostic reliability of individual stigmata or their combinations. Suggestive mongoloid facies have been observed in otherwise apparently normal individuals, as well as examples of mongolism in individuals who lack many other such common stigmata. Such apparent inconsistencies undoubtedly are related to varying clinical experiences as well as to variations in the syndrome itself.

Cummins[1] described certain differential trends of variation in the palmar dermatoglyphics of mongoloid individuals, and it occurred to us that these features might be useful in clinical practice.

Dermatoglyphics have a peculiar value as constitutional signs. Epidermal ridges are differentiated during the third and fourth fetal months;[2] their alignments and specific configurations are determined definitively as the ridges form, and in these respects the dermatoglyphics reflect developmental conditions existing in the organogenetic or early prenatal period. When distinctive trends of variation occur, as in mongolism, they are thus valid indicators at any period of life thereafter. In a preliminary test,[3] there was agreement of clinical and dermatoglyphic diagnoses—accomplished independently—in about 92% of 83 cases examined. This is a report on a larger series, drawing some comparisons as to frequency or reliability of dermatoglyphic features as contrasted with other evidences of mongolism, and describing technics and sources of error involved in procedures for securing and interpreting hand prints.

MATERIAL AND METHODS

Material for this study consists of 275 decipherable sets of prints secured from 278 individuals by 82 different physicians; 157 sets were secured from 160 patients considered to have typical clinical features of mongolism, 54 were from patients for whom the clinical diagnosis of mongolism was questionable, and 61 were from nonmongoloid controls;* 3 sets from clinically typical mongoloids were not decipherable.

Prints usually were submitted in batches, each set identified only by name or number, and were interpreted with no previous information as to referring physicians' clinical impressions or diagnoses.

TECHNIC

The making of hand prints is a simple process, yet it is one that must be carried out with care to secure clear, decipherable impressions. A satisfactory print, whether for identification, the study of mongolism, or some other applications of the dermatoglyphics, presents a clear registration of the

---

From the Departments of Anatomy and Pediatrics, Tulane University School of Medicine, and the Charity Hospital of Louisiana at New Orleans, La.

(Received for publication May 16, 1949.)

* This group is made up of 39 apparently normal individuals, 6 cretins, 2 microcephalic idiots, 1 patient with congenital toxoplasmosis, and 9 children with severe degrees of congenital cerebral defect or birth injury.

summits of epidermal ridges over the area to be examined—in the present instance, both right and left palms in their entirety. Accordingly, the prints should be examined as they are made; faulty ones should be saved since a complete reading of a palm may be possible in the combination of several regionally defective impressions.

The traditional practice is to spread a thin film of fingerprint ink on a glass plate, using a rubber roller, and then to ink the palm by contact with the spread film, finally pressing it against paper. Moistness of the subject's hands and the use of an excessive amount of ink are to be avoided as the principal causes of smudged prints. For maximum clarity of impressions, the paper should have a surface comparable in smoothness to that of good book paper. Pond gives a detailed account of procedure in printing the hands of infants by the ink method.[4]

Fingerprint ink is of about the same consistency and composition as printers' ink. If the cleansing necessary after its use and the chance of accidental soiling are regarded as objectionable, prints may be made with a specially sensitized paper. Such paper, as well as materials for ink printing, is obtainable from dealers in equipment and supplies for identification offices.*

Interpretation

Basic orientation of the palmar dermatoglyphics may be obtained elsewhere;[5] certain generalities may be emphasized here. We are concerned in this report only with the dermatoglyphics—the epidermal ridges and their configurations; flexion creases, including the "simian line" which has an increased frequency in mongolism, are not components of the dermatoglyphics. The palmar dermatoglyphics, like features more familiar in fingerprints, are variable among individuals. However, variations upon which individual identification ultimately depends are expressed in single ridges and other details that lie outside our present application. The ground plan of the palmar dermatoglyphics is expressed with fair consistency in all individuals, and variations concerned in the analysis of mongolism are of gross order, being differences of generalized configuration. Mongoloids differ from nonmongoloids of their own racial stock only in the frequencies of particular features that are common to the human species rather than by the possession of morphologic characters peculiar to them.[5, 6] Of the fingerprint patterns, for example, whorls are less frequent in mongoloids; however, it is necessary to resort to features in which individual expressions are more consistent, if they are to be utilized as diagnostic criteria.

Two such features were selected as the more promising diagnostic criteria, not only because of their high frequency in the first series of mongoloids examined but especially in view of the simplicity of their examination: 1. Extreme transversality of ridge courses in the distal territory of the palm was a conspicuous characteristic, not only as evidenced in the collective quantitative data[7] but also as they are apparent on inspection of individual palms. 2. A triradius situated in the central area of the palm was much more frequent than in nonmongoloids, with its extended radiants embracing a broad pattern or arch-shaped system of ridges over the hypothenar zone.

A set of prints presenting both of these features, either unilaterally or bilaterally, was recorded as positive for palmar signs of mongolism. When only one of these features appeared, the reading was recorded as "questionable"; it may be noted that the most common situation in such cases was the occurrence of marked transversality in the absence of a central triradius and an expanded hypothenar configuration. Negative readings were recorded for cases in which neither hand presented the features (Figs. 1 and 2).

Along with the interpretation of the dermatoglyphic features, a questionnaire to be filled out was returned to the referring physician. The data of Tables I, II, and III were derived from a study of these questionnaires and the hand prints. It is undoubtedly true that certain variations in interpretation of individual stigmata might be related to the age of patients in question or to the experience and training of physicians who filled out the forms, but this study was designed especially to test the validity and usefulness of this diagnostic aid in everyday practice; therefore, these clinical diagnoses and interpretations were accepted at face value.

While there can be no doubt that faulty clinical diagnoses may have been responsible for some discrepancies, especially in clinically questionable cases, it was considered that the study had added significance for this very reason—clinical diagnoses were made independently by 82 different physicians.

* Institute of Applied Science, 1920 Sunnyside Avenue, Chicago 40, or Faurot, Inc., 299 Broadway, New York 17.

Observations

Some incidental information was secured and is included in Table I. As to maternal age: This was significantly higher at the time of birth of a mongoloid individual than it was for nonmongoloid controls (P = less than 0.0001), although the differences were not as great as those noted by Bleyer in a much larger group.[8]

As to birth order: Average maternal parity, calculated with the mongoloid patient, was about the same for the three groups considered; this again cast doubt on the role of birth rank or "reproductive exhaustion" as causative factors in mongolism.

As to abnormalities in the first trimester of pregnancy: These were encountered more than twice as frequently in pregnancies which terminated with the birth of a mongoloid patient as they were among pregnancies resulting in questionable cases or nonmongoloids; abnormalities were encountered in 27.0% of the pregnancies in the first group, 11.3% of those in the second and 13.1% of those in the third. These differences are of borderline significance (P = .07). Due to the wide range in ages and birth order of the subjects included in this study, and consequent variable degrees of accuracy of maternal recollections for events early in pregnancy, some of these data might be questioned. There seems

TABLE I

Incidental Observations

	Mongoloids		Questionable Mongoloids		Nonmongoloid Controls	
Maternal Age, yrs. (range, 15 to 47)	No.	Per Cent	No.	Per Cent	No.	Per Cent
Less than 20	5	4.1	3	7.3	4	12.9
20–29.9	42	34.7	20	48.8	21	67.7
30–39.9	52	43.0	12	29.3	6	19.4
40 or more	22	18.2	6	14.6	0	0
Total, maternal age known:	121	100.0	41	100.0	31	100.0
Average yrs.:	32.2		29.4		24.2	
Birth Order (range, 1 to 15)						
1st	47	32.4	19	38.7	25	50.0
2nd	29	20.0	13	26.5	9	18.0
3rd	20	13.8	6	12.3	7	14.0
4th	12	8.3	0	0	4	8.0
5th or over	37	25.5	11	22.5	5	10.0
Total, birth order known:	145	100.0	49	100.0	50	100.0
Average parity with patient:	3.2		3.6		3.1	
Abnormalities, in 1st Trimester						
Threatened abortion	13	10.3	2	4.5	2	5.3
All others*	21	16.6	3	6.8	3	7.8
None	92	73.0	39	88.6	33	87.0
Total known	126	100.0	44	100.0	38	100.0

* Infections, injuries, diabetes, syphilis, structural abnormalities of uterus.

TABLE II

FREQUENCY OF SOME FEATURES IN MONGOLISM

	In Typical Mongoloids			In Questionable Mongoloids			In Nonmongoloid Controls		
	Total No. Observed	Per Cent Positive	Per Cent Quest.	Total No. Observed	Per Cent Positive	Per Cent Quest.	Total No. Observed	Per Cent Positive	Per Cent Quest.
1. Slanting eyes and/or epicanthi	160	96.9	2.5	53	37.7	34.0	61	8.2	14.8
2. Mental retardation*	120	93.3	6.7	44	38.6	59.1	59	13.6	20.3
3. Flattened bridge of nose*	149	92.6	5.4	52	44.2	23.1	61	21.3	6.6
4. Small rounded head with flat occiput	154	89.6	5.8	51	27.5	25.5	60	6.6	5.0
5. "Stubby" fingers	145	86.2	6.2	49	30.6	14.3	59	15.3	11.9
6. Palmar dermatoglyphics	157	85.3	9.6	52	42.3	11.5	61	13.1	9.8
7. Hypotonia of muscles	156	85.3	6.4	53	47.2	22.6	61	18.0	4.9
8. Hyperflexible joints	150	82.0	9.3	53	43.4	20.8	59	15.3	5.1
9. Small, curved little fingers	147	80.3	7.5	50	36.0	18.0	58	22.4	6.9
10. Widely set thumb and great toe	124	75.8	11.3	50	14.0	22.0	58	12.1	5.2
11. Short limbs	138	73.2	12.3	51	13.7	19.6	57	3.5	8.8
12. Delayed dentition*	97	72.1	10.3	36	36.1	5.5	56	12.5	7.1
13. Misshapen "simplified" ears	127	66.9	17.3	48	16.7	12.5	57	5.3	10.5
14. Stunted growth*	122	63.9	9.1	49	18.4	18.4	60	6.7	16.6
15. Dry skin	148	56.1	14.2	51	13.7	7.8	61	3.3	6.6
16. Enlarged tonsils and adenoids*	135	52.5	7.4	52	26.9	17.3	59	18.6	8.5
17. Faulty dentition*	77	51.9	10.4	34	17.6	11.8	53	7.5	1.9
18. Inelastic skin	141	48.2	13.5	51	9.8	9.8	60	1.7	5.0
19. "Simian lines" in palms	88	34.1	0	38	5.3	0	62	4.8	0
20. Congenital heart disease	152	33.6	7.9	50	12.0	10.0	61	1.6	1.6
21. Transverse fissures of tongue	122	29.5	10.7	45	6.7	4.4	57	3.5	0
22. Undescended testis(es)	81	24.7	6.2	21	14.3	0	34	2.9	2.9
23. Blepharitis	143	23.8	6.3	50	8.0	2.0	58	0	1.7
24. Strabismus	146	21.9	8.2	49	14.3	10.2	60	3.3	5.0
25. Nystagmus	147	21.1	6.8	51	1.9	3.9	61	4.9	1.6
26. Speckled irises	107	13.1	9.3	43	2.3	2.3	55	5.5	1.8
27. Fissures of lips	110	9.1	5.5	44	2.3	4.5	56	0	0

* These observations undoubtedly influenced by age of patients.

little doubt, however, that the differences would appear even greater had completely trustworthy and accurate information been available, or had the size of the control group been larger. In addition, several mothers in each of the three groups had had more than one of the conditions we chose to tabulate, i.e., threatened abortion and also syphilis, threatened abortion and also diabetes, etc., but we included only one abnormality for each in our calculations. Information gained even from this small sample indicates that abnormalities in the first trimester of pregnancy are important, at least as to the frequency with which they are associated with the occurrence of mongolism.[9, 10]

TABLE III

CLINICAL AND DERMATOGLYPHIC DIAGNOSES AS TO MONGOLISM COMPARED, IN 270 INDIVIDUALS

Clinical Diagnosis	Dermatoglyphic Diagnosis			Total
	Positive	Questionable	Negative	
Positive	134	15	8	157
Questionable	22	6	24	52
Negative	8	6	47	61
TOTAL	164	27	79	270

Clinicians appreciate that no single feature of mongolism is diagnostic in itself, but that several of them must occur together in the same individual in order to establish a diagnosis. The relative frequency of stigmata recorded by 82 qualified physicians therefore seemed to be of interest, and the signs were tabulated in order of their frequency in mongoloid individuals (Table II).

Because the total number of observations included in individual questionnaires varied considerably, it was necessary to consider the frequency of individual stigmata on a percentage basis; undoubtedly, the frequency of some of these stigmata was influenced to a large extent by age of the patients.

Clinical and dermatoglyphic diagnoses are compared in Table III.* It was of interest to note that our arbitrary designations for positive dermatoglyphics were fulfilled in 85% of patients with positive clinical diagnoses, and that positive or questionable dermatoglyphics appeared in almost 95% of those included in this clinical group. Most of the discrepancies, of course, were noted in the questionable groups; it was found that more than a third of the individuals included in this clinical category were under six months of age. Reappraisal of the clinical features which entered into these diagnoses and a study of follow-up reports from re-examination of these 52 infants and children for whom questionable clinical diagnoses were rendered will be the subject of another study.

Although the occurrence of positive or questionable dermatoglyphic features among patients for whom no clinical suspicion of mongolism existed gave rise to interesting genetic and embryologic speculation, it does not seem to have important clinical implications. The appearance of unequivocally positive or questionable dermatoglyphic patterns in otherwise normal individuals should have no more significance alone than do a number of other individual stigmata so frequently encountered in normal individuals. In other

* If the agreements of Table III occurred by chance, the probability of the observed distribution would be infinitesimally small.

* These observations undoubtedly influenced by age of patients.

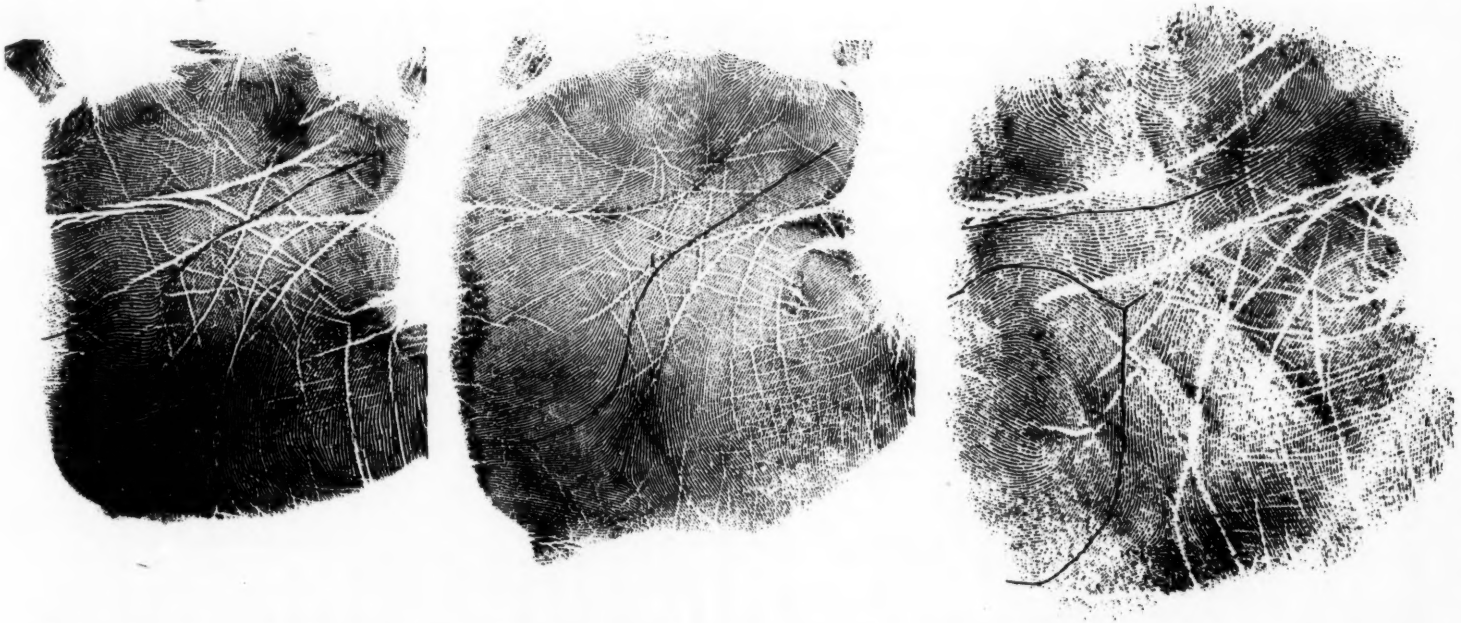

FIG. 1. Palm with no signs of mongolism. Note general diagonal slant of ridges in territory of traced line, which is known as line A in descriptive morphology. Beginning of this line is indicated by fixed landmark, triradius found in close relation to base of index finger; it is called "digital triradius *a*" in descriptive morphology. There is a triradius (proximal axial triradius) in proximal region of palm, but none in central area. Diagonal slant of palmar ridges and lack of centrally placed triradius constitute negative signs of mongolism; these 2 features are to be contrasted in Figs. 3-5.*

FIG. 2. Negative palm, with negative character accentuated by still greater slant of traced line.

FIG. 3. Palm showing both cardinal signs: marked transversality of ridges in distal territory and triradius situated in central area. Associated with triradius there is expansive loop pattern, but specific character of configuration in hypothenar area is widely variable in different cases (compare Figs. 4 and 5).

* This and all succeeding figures are from prints of left palms, with features critical to interpretation traced as pencil lines. Magnification X1.

* This and all succeeding figures are from prints of left palms, with features critical to interpretation traced as pencil lines. Magnification X1.

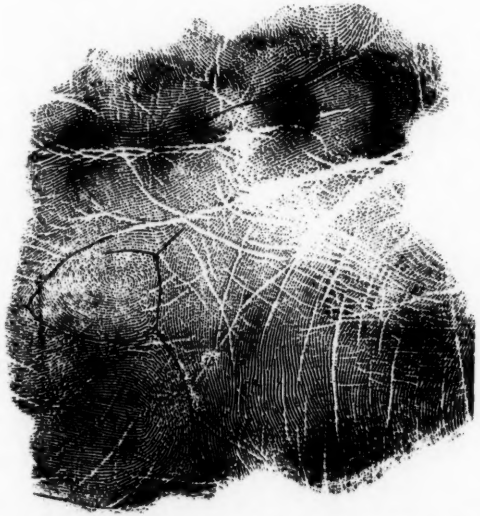

FIG. 4. Palm showing both cardinal signs. Hypothenar configuration is duplex pattern.

FIG. 5. Palm showing both cardinal signs and "simian line" in addition. Hypothenar configuration is an expansive arch rather than a more complex patterning as in Figs. 3 and 4.

words, while dermatoglyphics appear to have substantial value in diagnosis, they certainly are not diagnostic per se.

Conclusions

It has been demonstrated that characteristic dermatoglyphic changes rank high in frequency among the variable stigmata which go to make up the syndrome of mongolism. Though they are not diagnostic alone, it is believed that these objective, measurable and unchanging evidences of mongolism seen in hand prints should be helpful in establishing an early diagnosis. Positive dermatoglyphics rank high in frequency among stigmata reported in typical examples of mongolism by 82 physicians. The technic for preparing prints is a simple one which requires very little practice for perfection; interpretation based on the empiric but definite criteria defined can be accomplished with relative ease. A series of five prints are reproduced.

These findings are in keeping with the suggestion that factors responsible for the occurrence of mongolism are operative prior to the third month of fetal life, and are consistent with known facts concerning embryologic development of epidermal ridges of the palms.

References

1. Cummins, H., Dermatoglyphic stigmata in mongoloid imbeciles, Anat. Rec. **73**:407, 1939.
2. Gould, E. S., Unpublished thesis, Tulane University, 1948.
3. Cummins, H., and Platou, R. V., Mongolism: Objective early sign, South. M. J. **39**:925, 1946.
4. Pond, C. P., Positive and permanent identification of newborn, Illinois M. J. **69**:327, 1936.
5. Cummins, H., and Midlo, C., Finger prints, palms, and soles: Introduction to dermatoglyphics, Philadelphia, The Blakiston Company, 1943.
6. Snedeker, D. M., Study of palmar dermatoglyphics of mongoloid imbeciles, Human Biol. **20**:146, 1948.
7. Cummins, H., Bimanual asymmetry of palmar main lines, Quart. Phi Beta Pi Medical Fraternity **39**:4, 1942.
8. Bleyer, A., Role of advanced maternal age in causing mongolism, Am. J. Dis. Child. **55**:79, 1938.
9. Ingalls, T. H., Etiology of mongolism, Am. J. Dis. Child. **74**:147, 1947.
10. Benda, C. E., Prenatal maternal factors in mongolism, J.A.M.A. **139**:979, 1949.

Spanish Abstract

Dermatoglificos Palmares eu Mongolismo

Ha sido demonstrado ampliamente que alteraciones características dermatoglificas se colocan entre los mas frecuentes estigmos que hacen el syndrome reconocido como Mongolism. Aunque no son diagnosticos solos, creemos que estas evidencias objetivas, mensurables e inalterables valen mucho en el diagnóstico temprano. Dermatoglificos positivos se colocan entre los mas frecuentes estigmos mencionados como ejemplos típicos de Mongolism por ochenta y dos medicos. La téchnica para preparar las impresiones de las manos es muy fácil y necesita poca práctica para hacerla perfectamente; la interpretación fundado en emperico aunque definitivo criterio que hemos describido se puede hacer facilamente.

Estos resultados concuerdan con la sugestion que los factores responsables para la ocurrencia de Mongolism operan antes del tercer mes de la vida del feto y concuerdan con factos ciertos acerca del desarrollo de las arrugas epidérmicas de las manos.

1430 Tulane Avenue

STUDY OF CARDIAC ENLARGEMENT IN INFANCY WITH CASE REPORTS OF REVERSIBLE ENLARGEMENT

By HYMAN GREEN, M.D., AND JOHN APLEY, M.D., M.R.C.P.
Boston

THIS paper is concerned primarily with cardiac enlargement in infancy and its reversibility but studies on the incidence and etiology of other forms of cardiac enlargement are described also.

If cases with developmental malformations are excluded, it has been generally accepted that considerable enlargement of the heart in infants is not compatible with long life.[1-3] Cases are reported in this paper to show that enlargement can be reversible and the expectation of life can be unaffected. The reversibility of cardiac enlargement in general is discussed.

Investigations were undertaken to determine the incidence and etiology of neonatal cardiac enlargement, including the reversible forms. Chest roentgenograms of 1000 infants, taken in the first few days of life, were examined to obtain information regarding incidence. In two of these enlargement was reversed. The diagnosis and fate in 16 cases with cardiac enlargement is discussed. Data concerning etiology were derived from an analysis of postmortem findings in neonates in whom cardiac enlargement was found after death.

CASE REPORTS

Case 1: Mother's prenatal course was complicated by separation of the pubes and by peripheral pain in the legs. She received a well balanced diet.

Patient was a boy, normal delivery, birth wt. 3.2 kg., who appeared to thrive until a few weeks of age. Abdominal distension developed at 3 mos. of age. During the course of gastrointestinal fluoroscopy, the heart was seen to be enlarged. A 7 foot roentgenogram (fig. 1) confirmed this finding and showed enlargement mainly to the right (transverse cardiac diameter: 7.5 cm.—cardio-thoracic index: 0.61). Enlargement appeared considerable and, though the cardio-thoracic index just falls within the range included in 1 standard deviation above the mean for age, the transverse cardiac diameter is grossly in excess.[4] Physical examination revealed no murmurs or other abnormalities, ECG was normal and other laboratory data were within the normal range. He was said at this time to become "blanched" occasionally, but no cyanosis was observed.

Six weeks later there was no significant change either in physical or roentgenographic findings. On a 7 foot roentgenogram the cardio-thoracic index was 0.60, and transverse cardiac diameter 8.3 cm., a figure even more excessive than in the earlier film. ECG showed slight right-axis deviation.

At 6 mos. of age, he was progressing well, and a roentgenogram (fig. 2) showed the relative size of heart to be considerably reduced (transverse cardiac diameter: 8.3 cm.—cardio-thoracic index: 0.56).

At 1 yr. of age, though the chest had increased in size, the cardiac size (fig. 3) appeared not only relatively but actually smaller (transverse cardiac diameter: 8.1 cm.—cardio-thoracic index: 0.5). He was progressing favorably in every way, had trebled his birth weight, and showed no abnormal physical signs in the heart or elsewhere. ECG was normal.

He was re-examined at 18 mos. and at 2 yrs. of age when the heart was normal in size, and he was considered to be a healthy child. He has since developed well, and at the age of 11 yrs. shows no evidence of abnormality on examination.

Case 2: A boy, birth wt. 2.7 kg., with no relevant antenatal history. He was seen first at the age

From the Children's Medical Center and Lying-in Hospital, Boston, Mass.
(Received for publication May 18, 1949.)

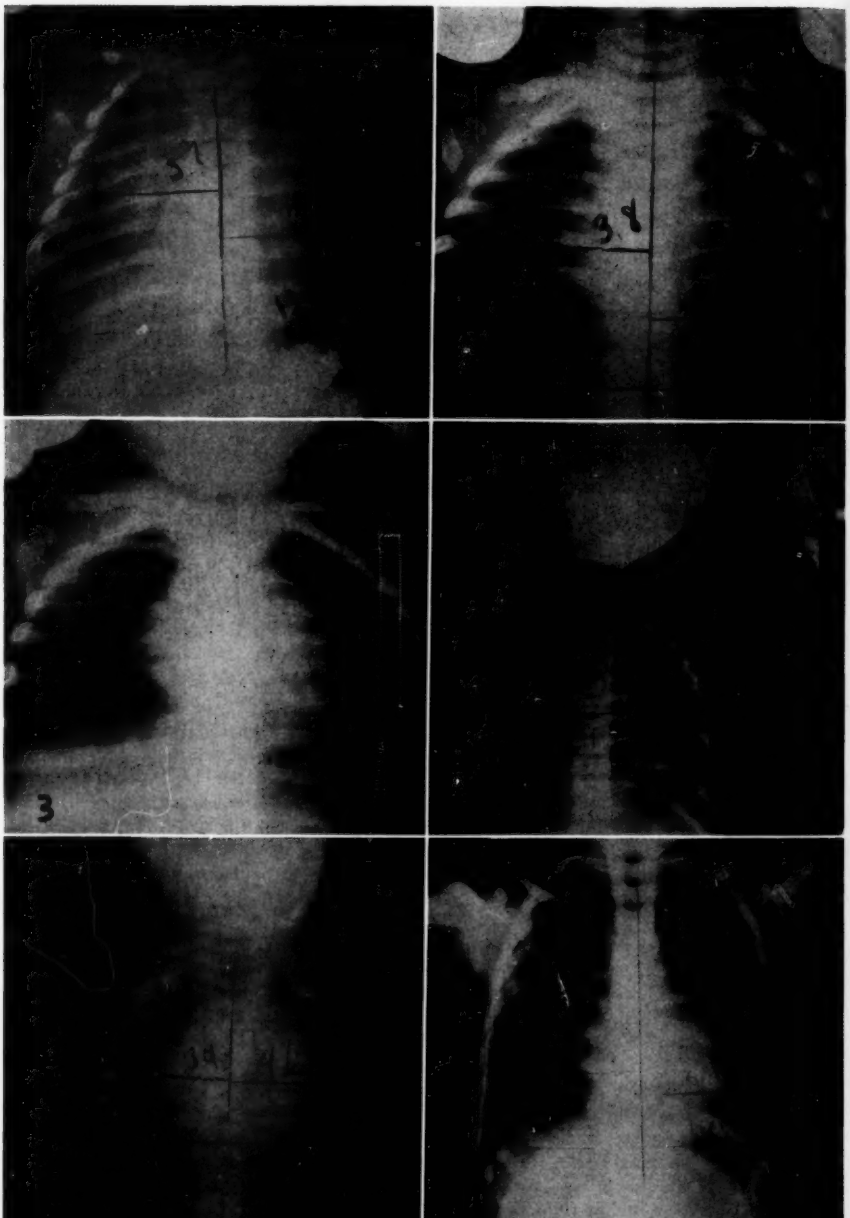

FIG. 1. Case 1 at 3 mos. FIG. 2. Case 1 at 6 mos. FIG. 3. Case 1 at 1 yr. FIG. 4. Case 2 at 3 mos. FIG. 5. Case 3 at 6 mos. FIG. 6. Case 3 at 10 yrs.

of 3 mos. because of bronchitis and congestion of the lungs since birth. He was small for his age; the only other significant clinical findings were cardiac enlargement and protrusion of the left anterior chest wall. A 6 foot roentgenogram (fig. 4) showed transverse cardiac diameter: 6.8 cm.—cardio-thoracic index: 0.6. Although these measurements of cardiac size fall within the upper limits of the normal range,[4] protrusion of the chest wall was taken to indicate a pathologic degree of cardiac enlargement. Tuberculin and other tests were negative.

On clinical examination at 6 mos., the heart appeared almost to fill the left chest; no roentgenogram was made. ECG was normal. For the next year he gained weight slowly. At 21 mos., heart was still enlarged, both clinically and roentgenographically. At 2 yrs. and 2 mos., heart was well within the normal range of size. (Transverse cardiac diameter: 7.5 cm.—cardio-thoracic index: 0.50.) ECG was also normal. At 3 yrs. of age, however, a systolic basal murmur became audible for the first time. One year later, though cardiac enlargement was no longer demonstrable, the left chest remained prominent. He still was not gaining weight satisfactorily at the age of 5 yrs.

During the next few years the murmur became less pronounced. He continued under observation until 11 yrs. of age. In the last 4 yrs. of this period no murmurs or other cardiovascular abnormalities were detected, but he remains a small, rather delicate-looking lad.

Case 3: A girl, birth wt. 2.1 kg., was delivered normally after an uneventful pregnancy. She gained weight slowly for some months after birth, and for several weeks prior to admission to the hospital at the age of 6 mos. she was not well. On examination she was found to present signs of rickets and bronchitis. A 6 foot roentgenogram (fig. 5) showed bony changes confirming the presence of rickets. It also showed asymmetric congestion of the lung fields characteristic of pulmonary inflammation and a grossly enlarged cardiac shadow (transverse cardiac diameter: 8.0 cm.—cardio-thoracic index: 0.71). Abnormal signs in the lungs cleared rapidly, but the cardiac enlargement persisted. ECG was essentially normal and a tuberculin test was negative. She continued under treatment but 3 mos. later was still in poor condition and the heart was still enlarged.

She was seen again at 2 yrs. of age, when an apical systolic murmur was audible. Bulging of the left anterior chest wall was now evident and persisted during the next 3 yrs. Thereafter, she continued to progress well and, when last seen at the age of 10 yrs., the only noteworthy finding on clinical examination was a short, faint, apical systolic murmur. By roentgenographic measurements (fig. 6), the cardio-thoracic index (0.54) exceeded the normal limits for age but the transverse cardiac diameter (8.8 cm.) was well within the normal range.[5]

Summary of Cases

In Case 1, cardiac enlargement was first observed at the age of 3 mos. Symptoms, which were presumably associated, had occurred for at least 2 mos. previously, and the enlargement may have originated at or near the time of birth. The cause of enlargement could not be established. The only clue was the nebulous one provided by the history of maternal illness, which at the time was suggested to be compatible with avitaminosis B. By the age of 1 yr., the heart had become normal in size and the child was continuing to make good progress when last seen at the age of 11 yrs.

In Case 2, the cardiac enlargement also came under observation for the first time when the child was 3 mos. old. The time of onset was probably at birth, in association with pulmonary infection which had continued to produce symptoms since that time. The extent of the enlargement appeared clinically to increase during the ensuing few months and was confirmed by protrusion of the chest wall. By 4 yrs. of age, the heart had become normal in size. All evidence of cardiac abnormality was eventually lost, though general physical development remained a little retarded at the age of 11 yrs.

In Case 3, enlargement of the heart was first detected at 6 mos. of age, in association with rickets and pulmonary infection of at least several weeks' duration. These conditions rapidly cleared up but the cardiac enlargement persisted long afterwards. The extent of the cardiac enlargement is emphasized in this case too by the protrusion of the chest wall. By the age of 10 yrs., the enlargement had completely receded and general development was unimpaired.

In none of these cases was significant anemia present. All were observed originally before the introduction of antibiotics and chemotherapy.

Discussion

Transient cardiac enlargement with recovery is quite common and will not be discussed. There is, however, in the literature a remarkable paucity of cases in which proved cardiac enlargement recovered after a considerable interval.

In some congenital malformations of the heart diminution of cardiac size, which may be real or relative, is occasionally seen. The diminution may be only apparent, as when slight enlargement becomes masked by natural alterations in the relative positions of the abdominal and thoracic viscera. Where true diminution occurs it has been suggested that it is due to such changes as obliteration of a septal defect or patent ductus arteriosus, but in many cases a specific diagnosis cannot be made. The following is an example:

Case 4: Cyanosis was present in infancy and repeated respiratory infections occurred. At 1 yr. of age, the heart was considerably enlarged and a systolic murmur was audible over the sternum. Slight clubbing of the fingers developed. At 6 yrs., basal systolic and diastolic murmurs were audible but the heart had become normal in size.

In the absence of congenital malformations, diminution of heart size may also occur after a considerable time. Keller[6] has described a case of interstitial myocarditis in which enlargement receded after many months. Similar changes may occur in paroxysmal tachycardia, beri-beri, severe anemia and in the infants of diabetic or prediabetic mothers.

From these cases it appears that a similar course of events may occur with pulmonary infection in early infancy, as in Cases 2 and 3. In Case 1 there was no evidence of pulmonary infection and a diagnosis of the underlying lesion could not be made.

It has long been known that recovery from hypertrophy, as distinct from dilatation, of the heart occurs. It must be presumed that cardiac enlargement which produces deformity of the chest wall is attributable to hypertrophy rather than to dilatation, and two at least of the cases fall, therefore, into the category of recovery from cardiac hypertrophy.

Incidence of Cardiac Enlargement in Early Infancy

It seemed desirable to estimate the frequency of occurrence of reversible enlargement in infancy. In order to determine the over-all incidence of all forms of cardiac enlargement, chest roentgenograms of 1,000 consecutive infants were made during the period of stay at the Boston Lying-in Hospital.

Clinical estimation of cardiac size in infants is unreliable and therefore was not done. The roentgenographic criteria of cardiac enlargement in the neonatal period have been defined by Bakwin and Bakwin[4] and by Caffey.[7] Considerable variations occur round the mean. During the first few days of life a transverse cardiac measurement exceeding 5.5 cm. on a film taken at a distance of 6 feet may be considered abnormal;[8] but apparent changes in size occur for many reasons and any rule is difficult to apply. In the series under review roentgenograms were taken at a uniform distance of 7 feet, and those cases were selected in which the heart appeared grossly enlarged.

Results

Cardiac enlargement was present in 16 of 1,000 infants examined roentgenographically. The fate of these cases is shown in Table I.

A postmortem examination was carried out in only two of the infants who died in the neonatal period. This omission was unavoidable and has been rectified as far as possible from the autopsy material described in the next section of this paper. In one of the two cases examined at post mortem an auricular septal defect was found; the other was a case of von Gierke's disease.

Seven survivors continued to be observed over a period of several years. In five, congenital heart disease was diagnosed on clinical and roentgenographic evidence: two were cases of septal defect, one had mongolism in addition, one case showed dextrocardia with additional anomalies and one was a case of tetralogy of Fallot. The two remaining case histories are summarized herewith:

TABLE I

16 CASES WITH CARDIAC ENLARGEMENT IN NEONATAL PERIOD*

Died in neonatal period: (1 case survived for 2½ mos.)	7	
Survived:	9	
Inadequate period of observation		2
Congenital cardiac malformations		5
Apparent recovery with normal heart		2

* As a guide to prognosis, it is of interest to compare the clinical features of those infants who died in the neonatal period and those who survived. The degree of cardiac enlargement varied unpredictably between the 2 groups; cardiac murmurs were audible in most cases of both groups, and neither their position nor character was of help in differentiation. The occurrence of cyanosis afforded a more reliable guide. Among the 7 infants who died, cyanosis was present in 4, developing at or soon after birth. Of the 9 cases who survived only 1 developed cyanosis, but this child continued under observation for an inadequate period. Cyanosis appears, therefore, to be an ominous sign if it occurs in association with cardiac enlargement.

Case 5: In addition to the roentgenographic finding of cardiac enlargement, the heart was manifestly enlarged by physical examination and a loud systolic murmur was audible, maximally at the base of the heart. At 2 mos. of age, the heart was only slightly enlarged roentgenographically and ECG was normal. General progress was satisfactory, but at 2 yrs. of age the murmur had become rougher in character. At the age of 4 the heart appeared within the normal limits of size roentgenographically, though a soft murmur was still to be heard.

Case 6: Both clinically and roentgenographically, the heart was considerably enlarged within a few days of birth. At 3 wks. of age, a systolic murmur was audible over the precordium, but was maximal in the left axilla. At 5 yrs., he had developed satisfactorily. Abnormal signs were not present then on physical examination; the heart was of normal size on roentgenographic examination, though the pulmonary segment showed a slight prominence seen frequently in normal children.

SUMMARY

The heart was considerably enlarged in 16 of 1,000 infants subjected to roentgenographic examination in the neonatal period. Seven of this group died shortly. Seven of the surviving cases continued under observation for several years: five had some congenital malformation of the heart, but in the remaining two cases the cardiac enlargement receded and no sign of any organic defect remained.

ETIOLOGY OF CARDIAC ENLARGEMENT IN NEONATES COMING TO AUTOPSY

It was considered that autopsy examination would provide the most accurate information concerning the etiology of all types of cardiac enlargement, including reversible forms. Accordingly, records and pathologic material were examined from 200 consecutive autopsies on infants born alive at the Boston Lying-in Hospital but dying in the neonatal period. Criteria based on weight are more reliable than those based on size, even though cases with pure dilatation may be excluded. Cases were selected from this series in which the heart weighed more than 25 gm. This figure of 25 gm. was selected to avoid inclusion of borderline cases, due to variations in technic and slight differences in age. A considerable number of cases with enlargement of lesser degree were thereby excluded.*

* In the main, there were cases with some form of pulmonary pathology or with erythroblastosis; only a minority had a congenital malformation of the heart.

In 29 of the 200 cases reviewed, the heart weighed more than 25 gm. The causes of death are listed in Table II.

It would be anticipated that intrauterine aspiration or atelectasis might be complicated by supervening infection, and in most cases a combination of more than one of the conditions enumerated occurred. Separation into individual types was therefore impracticable. In the tissue sections from this group, the cardiac muscle fibers were not hypertrophied, but in every case changes due to congestion and edema were apparent. These changes did not necessarily correspond in intensity to the degree of cardiac enlargement; thus, in the largest heart of the series (weight, 54 gm.), from a case of intrauterine aspiration with minimal pneumonic changes, cardiac congestion and edema were only slight.

TABLE II

CAUSES OF DEATH

Group 1. Pathologic lung conditions: (intrauterine aspiration, intrauterine infection, atelectasis, bronchopneumonia)	10
Group 2. Cardiac malformation: (multiple anomalies in most cases)	8
Group 3. Erythroblastosis fetalis	6
Group 4. Miscellaneous	5

Group 2 calls for no further description. Cardiac enlargement in fatal cases of erythroblastosis (Group 3) has long been recognized, but it is interesting to speculate whether it occurs to any significant degree in cases which survive. Among the miscellaneous cases (Group 4), one had previously been labelled "idiopathic cardiac hypertrophy"; microscopic changes associated with aspiration were, however, present in the lungs, though to a slight extent, and this case should more correctly be included in Group 1.

DISCUSSION

An unexpected result was the large proportion of cases with cardiac enlargement in which some pathologic condition of the lungs was present. Evidence of pulmonary infection was minimal in some cases; where infection occurred, it was frequently superimposed on intrauterine aspiration or atelectasis. The antenatal, natal or postnatal origin of the pulmonary lesion bore no evident relation to the degree of cardiac hypertrophy.

A significant feature of the analysis is the large proportion of cases in which cardiac malformations were absent. This is at variance with the concept that pathologic changes in the heart, occurring in the first few weeks of life, consist largely of developmental abnormalities.[9]

Milder forms of the conditions described may well be compatible with life and it seems justifiable to infer that the accompanying cardiac enlargement may persist for some time. It is therefore suggested that unexplained cardiac enlargement in the neonatal period may result from an undiagnosed pathologic process in the lungs.

As regards diagnosis, diseases such as erythroblastosis fetalis and cardiac malformations are, as a rule, readily excluded, but continued use of the term "idiopathic cardiac enlargement" implies some gaps in our knowledge. From the group of "idiopathic" hypertrophies several distinct entities have been separated, including von Gierke's disease, isolated myocarditis, aberrant left coronary artery and a formidable number of even rarer conditions,[1] though their diagnosis during life may prove impossible. Neely[10] has described

some cases of apparent "idiopathic" enlargement in which, at autopsy, an underlying interstitial pneumonitis was demonstrated. The evidence provided by our own cases supports Neely's contention inasmuch as the underlying cause of cardiac hypertrophy is frequently some pathologic process in the lungs. Recovery may, however, occur, and diagnosis during life may be possible in these cases.

Summary

Three cases are described in which cardiac enlargement in infants receded over a considerable period. In two of these cases, cardiac hypertrophy appeared to originate in association with pulmonary infection. Some other possible causes of reversible cardiac enlargement are discussed.

To determine the incidence of all forms of cardiac enlargement, including reversible enlargement, 1,000 infants were examined roentgenologically in the neonatal period. In 16 patients, considerable cardiac enlargement was present. Of these, seven died shortly. Among the nine survivors, two were lost sight of, five had a congenital malformation of the heart and two recovered with an apparently normal heart.

To investigate the etiology of neonatal cardiac enlargement, the material from 200 consecutive autopsies was reviewed. In 29 cases considerable hypertrophy of the heart was found: in eight of these a congenital malformation of the heart was present, six were cases of erythroblastosis fetalis and in five some miscellaneous cause produced the cardiac enlargement. In the remaining 10 cases some pathologic condition of the lungs was present.

It is suggested that some cases of cardiac hypertrophy are associated with pathologic lung conditions occurring before, during or after birth. The association is not necessarily fatal and the cardiac enlargement may prove reversible.

References

1. Kugel, M. A., Enlargement of heart in infants and younger children, Am. Heart J. **17**:602, 1939.
2. White, P. D., Heart Disease, New York, The Macmillan Company, 1944.
3. Levine, S. A., Clinical Heart Disease, ed. 3, Philadelphia, W. B. Saunders Company, 1945, p. 173.
4. Bakwin, H., and Bakwin, R. M., Body build in infants, Am. J. Dis. Child. **49**:861, 1935.
5. Maresh, M. M., Growth of heart related to bodily growth during childhood and adolescence, PEDIATRICS **2**:382, 1948.
6. Keller, H., Über idiopathische Myokarditis in Kindesalter und ihre Differentialdiagnose, Helvet. paediat. acta **1**:57, 1945.
7. Caffey, J., in Diagnostic Roentgenology, edited by Ross Golden, New York, Thomas Nelson & Sons, 1947, vol. 2.
8. Smith, C. A., Physiology of Newborn Infant, Springfield, Ill., Charles C Thomas, Publisher, 1945.
9. Potter, E. L., and Adair, F. L., Fetal and Neonatal Death, Chicago, University of Chicago Press, 1940.
10. Neely, J. M., Idiopathic cardiac enlargement occurring in infants and children, Ann. Int. Med. **15**:727, 1941.

Spanish Abstract

Estudio del Agrandamiento Cardíaco en Infancia con Informes de Caso de Agrandamiento Reversible

Se describen tres casos en los cuales el agrandamiento carfaco en infantes recedió durante un período considerable. En dos de estos casos, la hipertrofia cardíaca apareción originar en asociación

con infección pulmonar. Se discuten algunas otras causas posibles de agrandamiento cardíaco reversible.

Para determinar la incidencia de todas las formas del agrandamiento cardíaco, incluyendo el agrandamiento reversible, se examinaron 1000 infantes roentgenologicamente en el período neonatal. En 16 casos se presentó considerable agrandamiento cardíaco. De estos, siete murieron poco después; de los nueve que vivieron, 2 se perdieron de vista, cinco tuvieron una malformación congénita del corazón y dos se restablecieron con un corazón aparentemente normal.

Para investigar la etiología del agrandamiento cardíaco neonatal, se revisó el material de 200 autopsias consecutivas. En 29 casos se encontró considerable hipertrofia del corazón: en ocho de éstos se presentó una malformación congénita del corazón, seis fueron casos de eritroblastosis fetalis, y en cinco alguna causa miscelanea produjo el agrandamiento cardíaco. En los 10 casos restantes se presentó cierta condición patológica de los pulmones.

Se sugiere que algunos casos de hipertrofia cardíacos están asociados con condiciones patológicas del pulmón que ocurren antes, durante o después del parto. La asociación no es necesariamente fatal y el agrandamiento cardíaco puede ser reversible.

483 Beacon Street

CURRENT PROBLEMS IN DEATHS OF PERSONS UNDER 20 YEARS OF AGE

As Evidenced by a Study of the Situation in the Past Decade in New York City

By LEONA BAUMGARTNER, M.D., AND VIVIAN PESSIN, M.A.
New York City

MORTALITY rates for children in New York City, as elsewhere in this country, are on the decline. Such declines, however, are often taken for granted, which leads to a neglect of continuing studies of mortality. A periodic study of the problem, to discover changing trends and to point to problems demanding greater attention, seems definitely worth while.

For several reasons, analysis of New York City data is of more than local interest. The numbers are large; the deaths are, for all practical purposes, completely reported; and the cause of death as reported by the physician on the death certificate is verified by autopsy in a relatively large percentage of cases. It is of course always true that analysis of mortality trends as reflected in death certificates compares unfavorably in some respects with studies based on medical and hospital records. However, they are the only records which yield a picture of all the deaths occurring in a community.

The following data were secured by analyzing the confidential medical data on the death certificate[1] of every person under 20 years old who died in New York City in the 10 years from 1937 to 1946.*

MORTALITY BY AGE GROUP

The general downward trend in mortality is illustrated in Chart 1. This decline was only temporarily interrupted by the war, during which there was a small increase in the death rates of all age groups.

It is noteworthy that deaths of infants under 1 month of age have not declined as rapidly as those among children from 1 to 12 months of age. In the past 10 years, for example, there has been a reduction of 36% in infant mortality (deaths under 1 year) and only 19% in neonatal mortality (deaths under 1 month).

The over-all rate of decline in mortality is less than it was. For example, in the period from 1937 to 1946 there was a decline of 13% for all ages under 20, in contrast to the 47% decline for the same age groups from 1920 to 1930.

The medical and public health professions can well be satisfied with this record but

---

From the Department of Health of the City of New York, and from the New York Hospital and the Department of Pediatrics, Cornell University Medical College, New York, N.Y.

Presented at a meeting of the Pediatric Section of the New York Academy of Medicine, Feb. 13, 1948.

(Received for publication May 13, 1949.)

* In 1938 a revision was made in the International List of Causes of Deaths. Corrections for the minor changes in coding of the causes of death necessitated by this revision have been made in the figures used in this paper so that figures for 1937 and 1946 are comparable.

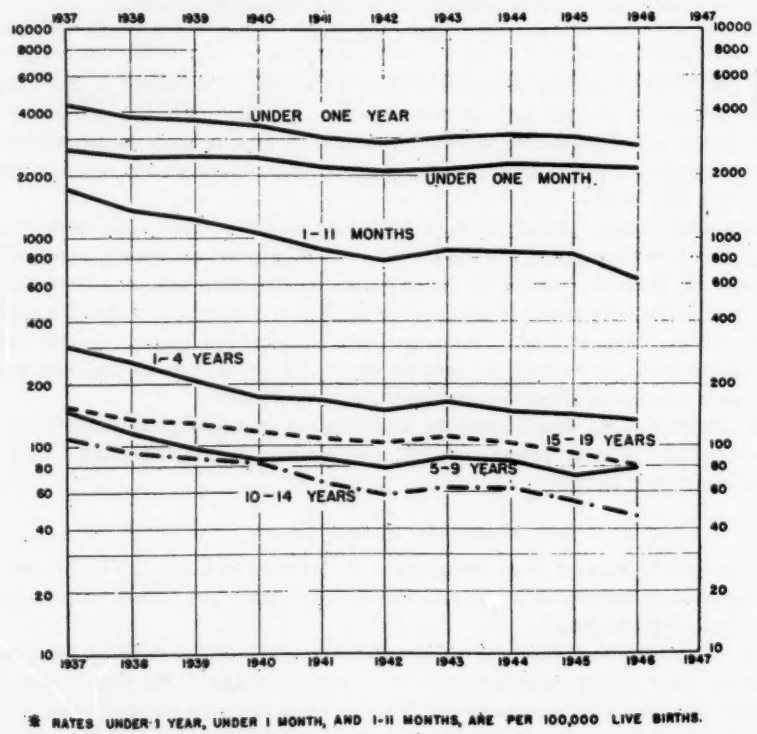

CHART 1

such satisfaction does not lead to further gains. To accomplish these, certain questions must be answered. What causes these deaths? Where is progress being made? What problems remain unsolved?

MORTALITY UNDER ONE YEAR OF AGE

For infants under 1 year of age, the mortality picture is clearly visualized in Chart 2. In this age group, prematurity, congenital malformation and birth injury stand out as today's chief problems. Ten years ago pneumonia, influenza and diarrheal diseases took a much greater toll than they do now. In 1946, these caused only 10% and 5%, respectively, of all deaths in this age group, while in 1937 the figures were 19% and 11%. It

is also evident from the chart that little progress has been made in reducing deaths attributed to premature birth and to congenital malformations. The decline in deaths due to injury at birth is probably attributable to better obstetric practice, though this has remained through the years the third leading cause of death. Deaths due to pertussis, though always small in number, have decreased markedly, with only five deaths in 1946 in infants under 1 year of age and 11 in those from 0 to 4 years of age.

It has often been pointed out that the notation "prematurity" on a death certificate does not necessarily reveal the true cause of death. However, the cause of death was verified by an autopsy in 40% of the infant deaths in this series—a higher percentage

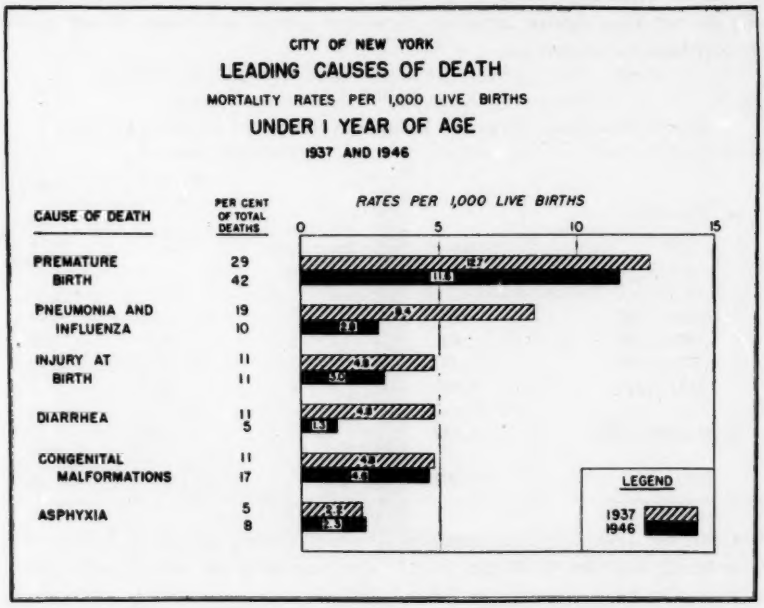

CHART 2

than prevails in many cities. It must be recognized, moreover, that many of the autopsies performed on infants are not satisfactory. When more careful autopsies are performed, it is revealed that many of the deaths now attributed to asphyxia, prematurity, etc., are due to more specific and often preventable causes, with infections playing a prominent part.[2]

All this, however, does not negate the fact that deaths associated with premature birth still constitute the major problem. As seen in Chart 2, prematurity increases in importance as a cause of death in infants as deaths from other causes are prevented, which is another way of saying that there has been least progress in fighting this particular cause of infant mortality. Moreover, about 50% of all deaths occur in so-called premature infants (i.e., those weighing less than 2500 gm. at birth) although the death may actually occur from other complications.

A large number of infant deaths occur in the neonatal stage. Of the 4,200 infant deaths in 1946, for example, 3,300, or approximately three quarters, occurred within the first

month of life. It is evident, therefore, that measures to reduce infant mortality must center mainly around the hospital and the care given the pregnant woman and the newly born, particularly the prematurely born, infant.

Further study of the prematurely born infant reveals several other points of interest. It is only since 1939 that birth weight has been recorded on birth certificates in New York City. The incidence of premature births in the period on record has run from 7.1 to 8.3%. Approximately 8.3% of all babies born alive weighed less than 2500 gm. in 1946. The total mortality rate among premature babies in the first year of life has varied from 18.4% in 1939 to 15.1% in 1946.* It has not been possible to compare this figure with statistics from other large urban areas or population groups which, because they usually do not keep figures according to weight groups and color, do not provide a satisfactory basis for comparison.

TABLE I

CITY OF NEW YORK: PREMATURE BIRTHS AND DEATHS, BY BIRTH WEIGHT, 1946

Birth Wt. (gm.)	Births		Deaths Under 1 Yr. of Age	
	No.	Per Cent of Premature Births	No.	Rate/100 Births
Under 1,000	593	4.7	549	92.6
1,000–1,499	827	6.5	470	56.8
1,500–1,999	2,173	17.2	425	19.6
2,000–2,499	9,051	71.6	467	5.2
Total under 2,500	12,644	100.0	1,911	15.1
Other wts.	140,092		2,328	1.7

Bain and her associates[3] have recorded a hospital fatality rate of 21.5 for 32,000 infants weighing less than 2,500 gm. in 323 American hospitals in 1945 and 1946. The New York City figures, as seen in Table I, include a larger percentage of babies in the upper weight groups in which mortality rates are usually low. This probably accounts for the lower mortality rate in New York City—though obviously the figures are not comparable anyway because one is based on deaths occurring during hospitalization and the other on deaths within the first year of life.

A comparison of mortality rates of prematurely born infants in different hospitals, or of the over-all city rate with an individual hospital, would obviously be of some interest; but such procedures are, for the most part, unsatisfactory from the statistical point of view. Allowance must be made, for example, for difference in economic status, in distribution of nonwhite and white babies, or in distribution of small and larger babies. The groups are usually too small to compare, and the comparative figures one often sees

* On a certain number of birth certificates, birth weight is not recorded. However, the period of gestation is stated. A method of distributing these "weight not stated" babies to weight groups by using the period of gestation has been devised. When these babies are included the incidence of prematurity is raised about 1% and the mortality figure in 1946, for example, to 19%. However, since figures are probably more easily compared when only the babies of known weight are included, these figures are presented in Table I.

are not statistically significant. The best we have been able to do is to compare the over-all city rate for 1946 with the rate for 1945 and 1946 in one rather large hospital which cares for white and Negro premature infants born in its own maternity service as well as some born elsewhere. If the mortality rate achieved by this hospital had applied to all infants prematurely born in the city in 1946, there would have been about 1,500 deaths instead of 1,900, a saving of about 400 infant lives.

About half of all neonatal deaths occur in the first 24 hours, and an additional third in the next six days. This is also true for the prematurely born infant. Some of these deaths are not preventable, but others are. It is certain that prolonging the life of the infant past the first 24 hours increases enormously its chances for survival.

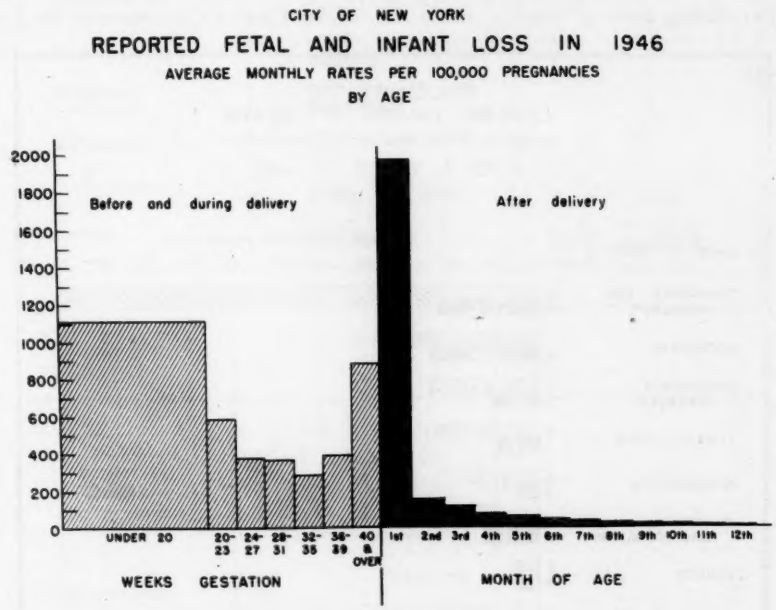

CHART 3

MORTALITY IN FETAL LIFE

If discussion of the possibility of saving additional lives is limited to the deaths of live-born infants, an important part of the problem as indicated in Chart 3 (showing deaths before and after delivery) is neglected. In 1946, about three times as many fetal deaths were reported as deaths of infants under one year of age. How much greater the pregnancy wastage is through unreported and illegal abortions cannot be known. Actually, whether a viable fetus dies a few minutes before or after delivery, there is still loss of life. The problem of the fetus that is not carried into the viable stage is similarly important to those interested in reducing infant mortality.

Certainly too little is known of the factors contributing to fetal deaths and to the deaths attributed to prematurity, congenital malformation and birth injury. Certain of the deaths occurring today can be prevented but many will not be until research laboratories discover

fundamental causes and effective methods of prevention. Such research is imperative if our general death rate is to continue downward. It is little realized that today deaths associated with childbirth (maternal, fetal and neonatal deaths) constitute a leading cause of death. In New York City, for example, fetal and neonatal deaths, numbering 16,259 in 1946, were the second largest cause of death for all ages, including those over 20. Only heart disease claimed a larger number (30,348).

Mortality From One to Four

Decrease in the mortality rate for this age group has been somewhat more rapid than in the infant group (see Chart 1), but the actual number of deaths involved is, of course, much smaller—only 663 in 1946, for example, compared to 4,200 for infants.

The leading cause of death is now accidents (see Chart 4), accidents in the home

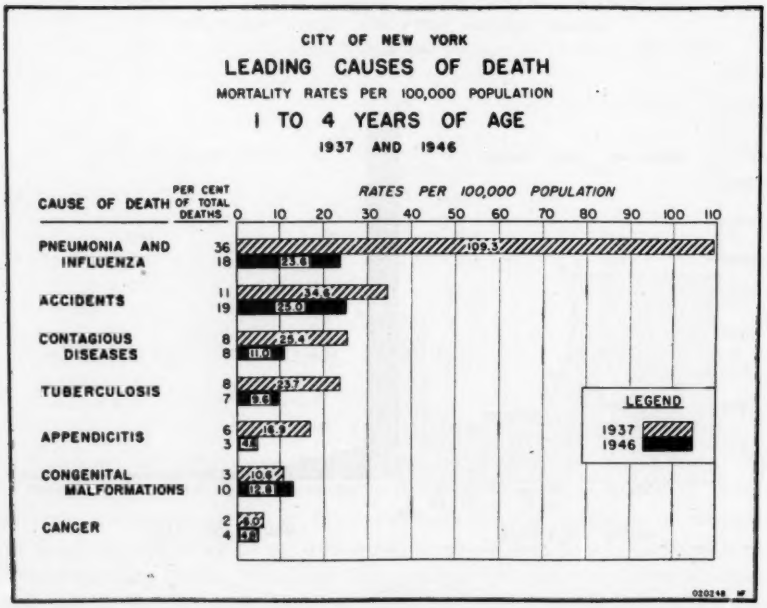

Chart 4

taking the majority of lives. This chart illustrates strikingly, as do the charts for other age groups, the rapid progress that has been made in the control of pneumonia and influenza. There is reason for satisfaction, too, in the 73% decline in mortality due to appendicitis and the 60% decline in tuberculosis and contagious diseases. The slight increases in death rates due to congenital malformations are related, of course, to an increasing ability to keep these children alive through the first year of life.

Mortality From Five to Nine

In this age group, too, accidents are the leading cause of death, as they were 10 years ago (see Chart 5). Children are now out on their own, and this is reflected in the number and type of fatal accidents that occur. Under 5 years of age, three fourths of all fatal

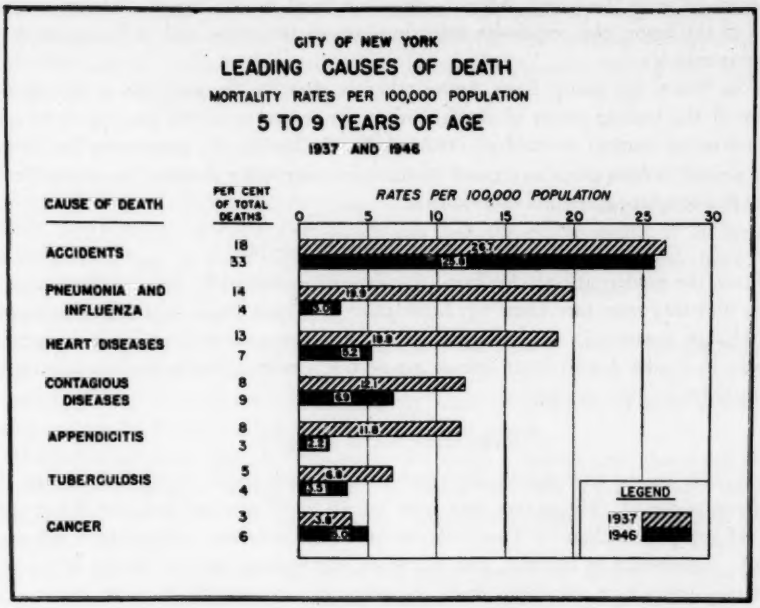

CHART 5

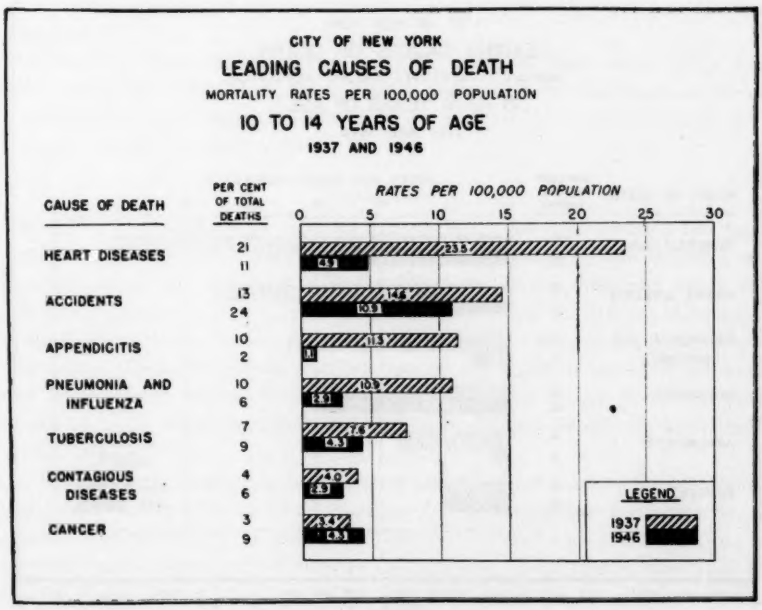

CHART 6

accidents occur in the home. After 5, only one third to one fourth of these accidents occur in the home, the remainder occurring outside the home and including those due to motor vehicles.

In the 5 to 9 age group, heart disease takes its place for the first time in the age cycle as one of the leading causes of death, and cancer jumps to fourth place with an actual increase in the number of children involved. On the credit side, pneumonia has dropped from second to fifth place as a cause of death and important declines are also evident in deaths due to appendicitis and tuberculosis.

Mortality From 10 to 14

This is the golden age of childhood if measured by mortality, for it is the age of the lowest mortality rates (see Chart 6). Large gains have been made in saving lives formerly lost through pneumonia and influenza, tuberculosis, appendicitis and heart disease. The declines in deaths due to heart disease are of the same magnitude if rheumatic fever is also included in this category.

Mortality From 15 to 19

It is well known that during adolescence death rates begin to climb again. In 1946 the jump is one of 76% as one goes from the 10 to 14 year old group to this 15 to 19 year old group (see Chart 7). Deaths due to tuberculosis increase sufficiently in this period of later adolescence to become, with accidents, the leading cause of death. In 10 years, of course, gains have also been made in saving the lives of those 15 to 19 years old. There are fewer deaths due to appendicitis, pneumonia, tuberculosis and heart disease in

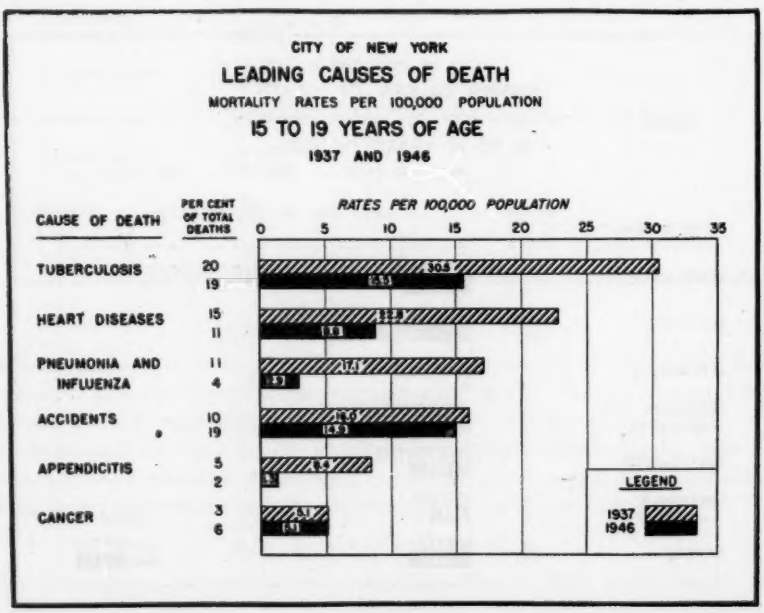

Chart 7

1946 than in 1937—even as in the younger children. The relatively insignificant change, through the years, in the rate due to accidents is, however, discouraging. Gains in saving lives lost through accidents in the younger age groups were greater, during the 10 years, than they were in this group of 15 to 19 year olds.

Other Problems

The physician of 40 years ago would no doubt be amazed to see that the so-called contagious diseases of childhood today play so small a role in mortality of those persons under 20. In 1946, for example, they caused less than 1% of the deaths of individuals up to 20 years of age. In 1900 they caused 14% of the deaths and by 1920 this figure had dropped to only 12%. This indeed is a battle that has been won.

What lies ahead? Four facts seem quite clear.

1. The greatest loss of children's lives occurs at or near birth. In fact the numbers are so large that, if compared to all causes of death at all ages in New York City, these rank second. In other words, the loss of life of viable fetuses and in early infancy is exceeded only by deaths due to diseases of the circulatory system.

2. There is insufficient scientific knowledge to prevent a considerable number of these infant deaths. Research as to the fundamental causes of death and the means of preventing them is more or less sporadic, is only meagerly supported financially, and needs to be greatly intensified.

3. Despite these lacks, much that is known about preventing deaths, particularly in newly born and prematurely born infants, is not put into practice in New York City today. If all newly born babies and mothers got the care that modern medicine is able to give, a large number of infant lives could be saved now. There is also sufficient knowledge to prevent a considerable number of deaths due to tuberculosis, pneumonia, influenza and appendicitis.

4. Accidents and heart disease emerge as leading causes of death after infancy. Gains are still to be made in preventing these deaths. There has been little study of the accident problem, and much research needs to be done before satisfactory measures can be found for the control of rheumatic fever.

Conclusion

In the past 10 years mortality rates for persons under 20 have declined less rapidly than in that of the previous decades. Nevertheless, the application of new and well recognized procedures in the prevention of deaths due to pneumonia, influenza, appendicitis, diarrhea and contagious diseases, and tuberculosis have led to striking reductions in deaths due to these causes. Because of these reductions, other causes of death have assumed new importance. Thus, in children over one year of age accidents are today the leading cause of death. Heart disease, tuberculosis and cancer claim a high percentage among those from 10 to 20, while contagious and respiratory diseases are still important in children under 10.

In infants, the deaths occurring before, at or near birth are of chief importance, with those associated with premature birth assuming an importance that demands active and immediate attention. Despite the gains made, deaths associated with childbirth (i.e., fetal and neonatal deaths) stand second today in claiming lives of all ages in New York City. Only heart disease has a larger mortality. The time has come for physicians to take cognizance of these facts and to see that all mothers and babies get the kind of care which

good pediatricians and obstetricians know can be given. In addition, there is a pressing need for an intensified research program to the end that deaths in infancy and those due to accidents and heart disease can more effectively be prevented.

REFERENCES

1. Duffield, T. J., Parker, Sylvia L., and Baumgartner, Leona, Birth weight and its relation to neonatal mortality, Child **5**:123, 1940.
2. Potter, Edith L., and Adair, F. L., Fetal and Neonatal Death, Chicago, University of Chicago Press, 1940.
3. Bain, Katherine, Hubbard, J. P., and Pennell, Maryland P., Hospital fatality rates for premature infants, PEDIATRICS **4**:454, 1949.

SPANISH ABSTRACT

Problemas Corrientes en Muertes de Personas Bajo 20 Años de Edad Como se Han Visto Mediante un Estudio de la Situación en la Decada Pasada en la Ciudad de Nueva York

Se hizo un estudio comparativo de la reducción en las proporciones de mortalidad para niños en la Ciudad de Nueva York de 1937 a 1946. Los certificados de muerte, archivados por los médicos allí, contienen ciertos informes médidos confidenciales y son estos informes los que se han usado como base para este estudio. Las proporciones de mortalidad para los siguientes grupos de edades son analizados: Menos de 1, 1-4, 5-9, 10-4 y 15-19 años. El número de muertes fetales queda incluído. Se indican las causas de muerte principales en cada grupo lo mismo que los cambios en su importancia relativa durante los años. Los autores concluyen:

En los últimos diez años las proporciones de mortalidad para personas de menos de 20 años han bajados menos rapidamente que las de las décadas anteriores. Sin embargo, la aplicación de procedimientos neuvos y bien reconocidos en la prevención de muertes debidas a neumonía, influenza, apendicitis, diarrea y enfermedades contagiosas, y tuberculosis han ayudado a reducir notablemente las muertes debidas a estas causas. A causa de estas reducciones, otras causas de muerte han asumido nueva importancia. Asi, en niños de más de un año de edad los accidentes son hoy la causa de muerte que va a la cabeza. Enfermedad del corazón, tuberculosis y cancer reclaman un alto porcentaje entre éstos de 10-20 años, mientras que enfermedades contagiosas y respiratorias son aún importantes en niños de menos de 10 años.

En infantes, las muertes que ocurren antes, durante o cerca del parto son de primordial importancia, con aquellas asociadas con parto prematuro que asumen una importancia que pide atención activa e inmediata. A pesar de las ganancias hechas, las muertes asociadas con el parto (i.e., muertes fetales y neonatales) ocupan segundo lugar hoy en reclamar las vidas de todas las edades en los ciudadanos de la Ciudad de Nueva York. Solamente la enfermedad del corazón tiene una mortalidad mayor. El tiempo ha llegado para que los médicos se den cuenta de estos hechos y vean que todas las madres y bebés reciban la clase de cuidado que los buenos pediátricos y obstétricos puedan darles. Además, hay una gran necesidad para un programa de investigación intensificado con el objeto de que las muertes en infancia y aquellas debidas a accidentes y enfermedades del corazón sean evitadas más eficazmente.

125 Worth Street

AUREOMYCIN IN THE TREATMENT OF EXPERIMENTAL AND CLINICAL INFECTIONS WITH H. INFLUENZAE, TYPE B

By CAROLINE A. CHANDLER, M.D., AND HORACE L. HODES, M.D.
Baltimore

STUDIES on the activity of aureomycin have shown it to be effective, *in vitro* and *in vivo,* against a wide variety of gram positive and gram negative bacteria.[1-3] The present study was undertaken to determine the effectiveness of aureomycin in the treatment of mice experimentally infected with H. influenzae, type B. It was further thought that, if the activity of this antibiotic compared favorably with that of other antibiotics known to be of value in the treatment of H. influenzae infections, clinical trial of aureomycin would be warranted. To this end, the following studies were carried out:

EXPERIMENTAL OBSERVATIONS

Methods

The organism used throughout the experimental part of this study was a type B influenza bacillus (Cox) isolated from the cerebrospinal fluid of a patient with H. influenzae meningitis. The susceptibility of this test strain to the various antibiotics used was determined in the following manner: Serial 2-fold dilutions of the antibiotics in Difco heart infusion broth (to which had been added 5% Filde's tryptic digest) were inoculated with equal volumes of an 18 hr. Filde's broth culture so diluted as to result in an inoculum of approximately 500 thousand organisms/ml. The tests were read at the end of 24 hrs.

Swiss, albino mice (CF1), weighing on the average of 20 gm. each, were inoculated intraperitoneally with 1.0 ml. of a mucin suspension of the test organism. When a large infecting dose was desired, the organisms were so diluted in mucin as to result in a suspension containing 50 million organisms/ml. When a small infecting dose was desired, the suspension was so diluted in mucin as to result in 75 thousand organisms/ml.

Solution of the antibiotics—aureomycin, polymyxin, streptomycin, dihydrostreptomycin and Q-19—were made up in sterile distilled water the day prior to each experimental run. Further dilutions of each drug to the desired concentrations were also made in sterile distilled water and the tubes were kept in the icebox throughout the experimental run. The mice were treated according to 2 schedules. According to the 1st, they were treated immediately postinfection, at 5 hrs. and again at 23 hrs. postinfection. According to the 2nd, treatment was given 1½ hrs. prior to infection and at 5 and 23 hrs. postinfection. All the drugs were administered subcutaneously in such concentration that the total fluid volume given at each injection was 0.2 ml. Groups of 10 mice for each dose of drug were used together with 10 control mice in every experimental trial. All mice were observed for a period of 8 days postinfection, for death or survival.

From the Departments of Preventive Medicine and Pediatrics, The Johns Hopkins University School of Medicine, and Sydenham Hospital, Baltimore City Health Department, Baltimore, Md.

These investigations were supported by a grant from Lederle Laboratories Division, American Cyanamid Company.

Based on findings presented before the Society for Pediatric Research, Atlantic City, N.J., May 1948.

(Received for publication May 1, 1949.)

Aureomycin and polymyxin (B-71) were supplied by the Lederle Laboratories Division, American Cyanamid Company. Dihydrostreptomycin was supplied by E. R. Squibb and Sons. Q-19 was supplied by The Upjohn Company.

Results

In vitro, aureomycin was found to be inhibitory to the test organism at a level of 0.625 μgm./ml. of medium, polymyxin at 0.625 μgm., streptomycin at 1.25 μgm., dihydrostreptomycin at 2.5 μgm., and Q-19 at 1.25 μgm./ml.

In mice infected intraperitoneally with mucin suspensions containing approximately 75 thousand organisms/ml., aureomycin was found to be as effective therapeutically as streptomycin and dihydrostreptomycin in doses of 20 mg. of drug/kg. body weight when given subcutaneously at 0, 5 and 23 hrs. postinfection. With this dosage schedule, the survival rate was 95% for all 3 of these antibiotics. The corresponding survival rates for polymyxin and Q-19 were 85% and 65%, respectively. When doses of 1 mg. and 5 mg./kg. body weight were given according to this same schedule, survival rates were as follows:

	1 mg./kg.	5 mg./kg.
Aureomycin	10%	35%
Polymyxin	75%	95%
Streptomycin	15%	60%
Dihydrostreptomycin	15%	40%
Q-19	5%	50%

These results are illustrated graphically in Chart 1.

When the infecting number of organisms was increased to 50 million organisms/ml. of mucin, and the initial dose of drug was given 1½ hrs. prior to infection (with the subsequent 2 doses again given at 5 and 23 hrs. postinfection), no mice survived treatment with streptomycin, dihydrostreptomycin or Q-19 in doses of 1, 5 or 20 mg./kg. body weight. In the case of aureomycin, 25% of the mice receiving 20 mg. of drug/kg. body weight survived, but none survived with doses of 1 or 5 mg./kg. With polymyxin, 40% of the mice receiving 20 mg. of drug/kg. body weight survived, but again none survived with doses of 1 or 5 mg./kg. These results are shown in Chart 1.

Clinical Observations

Because of these suggestive experimental results and because aureomycin has been found to produce essentially no toxic symptoms in man, treatment of patients with H. influenzae, type B, infections seemed indicated. To date, 2 patients with H. influenzae, type B, meningitis have been treated with aureomycin and sulfadiazine and 3 with aureomycin alone. The following case reports summarize the findings on these patients:

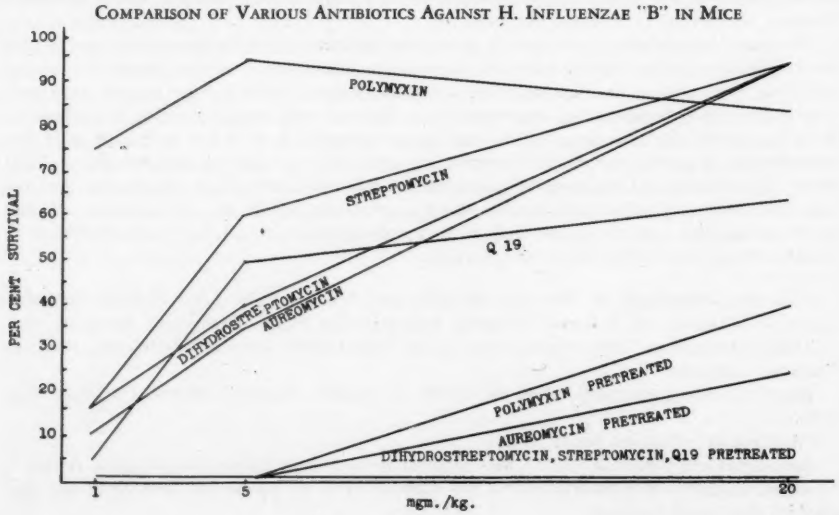

Chart 1

Case Reports

Case 1. S.C., a 27 mo. old white male, was transferred from the Naval Hospital, Annapolis, Md., to Sydenham Hospital, with the complaint of convulsions and fever of 2 days' duration. Immediately prior to admission, petechiae were noted on the buttocks.

Past and family histories were noncontributory.

Patient was well developed and nourished and weighed 15.4 kg. Face was flushed and he was lethargic but oriented. Temperature was 40°C. There were several petechiae on the buttocks, right wrist and back of the neck. Bilateral otitis media was present. There was an internal squint of the left eye. Tonsils were enlarged and inflamed. There was moderate nuchal rigidity. Kernig's and Brudzinski's reflex signs were positive. No deep reflexes could be elicited except for ankle jerks on the left. Abdominal and cremasteric reflexes were absent.

Laboratory examination: Hgb. 11.0 gm./100 cc., a WBC count of 13.75 thousand/cmm. with 73% leucocytes, 24% lymphocytes and 3% monocytes. Urine analysis was negative. Blood culture was positive for H. influenzae, type B. Lumbar puncture showed cerebrospinal fluid to be under increased pressure with a white cell count of 7.66 thousand/cmm. with 100% leucocytes, a positive Pandy, and only a trace of sugar. The smear showed gram negative rods that quelled with type B influenzal antiserum. Culture of the spinal fluid was positive for H. influenzae, type B.

On admission, the patient was given Na-sulfadiazine 750 mg. and aureomycin 50 mg. intraveneously, and aureomycin 125 mg. by mouth. Thereafter, he was given a daily dosage of aureomycin 100 mg. intraveneously for 6 days, and aureomycin 750 mg. orally for 13 days, making a combined total dosage of 10.35 gm. The total dose of sulfadiazine given was 14.25 gm. Within 24 hrs. after the institution of therapy, the temperature reached normal and the meningeal signs became less marked, but an internal squint developed on the right. Culture of the spinal fluid was still positive for H. influenzae on the day after admission, but thereafter remained negative until discharge. Except for an occasional slight elevation of temperature during the first week of his hospital stay, the patient made an uneventful convalescence and was discharged after 3 wks. as fully recovered. Aureomycin was well tolerated with no signs of toxicity.

Case 2. L.M., a 16 mo. old white female, was transferred from Sinai Hospital in Baltimore to Sydenham Hospital with the diagnosis of meningitis. Twelve days prior to admission, she developed fever, listlessness and rapid breathing. A diagnosis of pneumonia was made and penicillin therapy was begun. Treatment was continued until 6 days prior to admission. On the night before admission, she developed stiffness of the neck and screamed whenever she was moved. On the day of admission she was taken to Sinai Hospital where a lumbar puncture was done. A tentative diagnosis of H. influenzae meningitis was made on the basis of a smear of the cerebrospinal fluid and she was given penicillin 5000 u. and streptomycin 25 mg. intrathecally stat. She was then transferred to Sydenham Hospital. Past and family histories were noncontributory.

Patient was well developed and nourished and weighed 9.1 kg. She looked moderately ill, and held her head stiffly. Temperature was 40.3°C. Anterior fontanelle was firm. Neck was resistant to anterior flexion. There was slight impairment of resonance with diminished breath sounds over the base of the right lung. There was a soft systolic murmer at the apex and along the left sternal border. Liver edge was palpable 2 fingers' breadth below the costal margin. All reflexes except the knee jerks were present. Kernig's and Brudzinski's reflex signs were negative. The cranial nerves appeared to be intact.

Laboratory examination: Hgb. 10.0 gm./100 cc., WBC count 22.4 thousand/cmm. with 73% leucocytes, 23% lymphocytes and 4% monocytes. Urine analysis was negative. Blood culture was positive for H. influenzae, type B. Culture of the naso-pharynx was positive for pneumococcus, type 14. Lumbar puncture (performed at Sinai Hospital) showed the cerebrospinal fluid to be milky with a white cell count of 1.2 thousand/cmm. with a positive Pandy and no sugar. The smear showed gram negative bacilli that quelled with type B influenzal antiserum. Culture of the spinal fluid was positive for H. influenzae, type B.

On admission, patient was given aureomycin 50 mg. and Na-sulfadiazine 500 mg. intravenously, and aureomycin 125 mg. by mouth. Thereafter, she received a daily dosage of aureomycin 100 mg. intravenously for 6 days, and aureomycin 500 mg. orally for 14.5 days, making a combined total dosage of 7.85 gm. Total dose of sulfadiazine given was 24.25 gm. Within 24 hrs. after the institution of therapy, temperature reached normal and the patient continued to be afebrile throughout the rest of her hospital stay. Both blood and spinal fluid cultures became negative on the day after

admission and remained negative thereafter. All meningeal signs disappeared within 72 hrs. and at discharge the patient had made a complete recovery with no signs of residual damage. There were no evidences of drug toxocity at any time.

Case 3. F.L., a 2½ yr. old Negro female, was transferred from the Harriet Lane Home to Sydenham Hospital, with the diagnosis of H. influenzae meningitis.

Past and family histories were noncontributory.

Nine days prior to admission, she developed fever, anorexia and wheezy breathing. She was given sulfadiazine 1½ gm. daily for 3 days. Temperature fell to normal and she seemed essentially recovered until the evening before admission when her temperature rose to 38.3°C. and her neck seemed stiff. On the morning of admission, she was seen in the Harriet Lane Home, where a lumbar puncture was performed. A smear of the spinal fluid showed gram negative rods which quelled with H. influenzae, type B, antiserum. She was transferred to Sydenham Hospital.

Patient was well developed and nourished in no acute distress. She was irritable and resisted being moved, but was otherwise alert and cooperative. Temperature was 39.6°C. There was marked nuchal rigidity. All reflexes were hyperactive. Brudzinski's, Kernig's and Babinski's reflex signs were negative.

Laboratory examination: Hgb. 9.0 gm./100 cc., WBC count of 13.4 thousand/cmm. with 96% leucocytes and 4% monocytes. Urine analysis was negative except for a 3+ acetone. Blood culture was negative for H. influenzae, type B. Lumbar puncture showed the cerebrospinal fluid to be slightly cloudy with a white cell count of 700/cmm. with 80% leucocytes, a positive Pandy, and a moderate decrease in the sugar content. The smear showed gram negative rods that quelled with type B influenzal antiserum. Culture of the spinal fluid was positive for H. influenzae, type B. *In vitro,* the growth of this organism was inhibited by aureomycin 0.6 µgm./cc. broth.

On admission, patient was given aureomycin 50 mg. intravenously and 125 mg. by mouth. Thereafter, she was given a daily dosage of aureomycin 140 mg. intravenously for 9 days and 750 mg. orally for 14 days, making a combined total dosage of 12.9 gm. Although she showed marked clinical improvement within 24 hrs., cultures of her spinal fluid remained positive for 6 days after therapy was instituted. The level of aureomycin in the spinal fluid was determined on 3 separate occasions during this period and was found to range from 0.1 to 0.4 µgm./cc.

Determinations of the susceptibility of the H. influenzae isolated from the spinal fluid on 5 successive days showed that the organism continued to be inhibited by aureomycin 0.6 µgm./cc. broth.

Patient's temperature, which fell initially from 40°C. to 37.3°C. within 24 hrs. after the institution of therapy, continued to spike to around 38.3°C. for the first week in the hospital. Thereafter, she remained afebrile and progressed rapidly to complete recovery. Except for the vomiting of 2 oral doses of aureomycin when therapy was first begun, there were no evidences of drug toxicity.

Case 4. R.B., a 2 yr. old white male, was admitted to Sydenham Hospital with the diagnosis of meningitis.

Past and family histories were noncontributory.

Forty-eight hours prior to admission, he was seen by a physician because of vomiting and a temperature of 40°C. He was given penicillin and a sulfonamide was also prescribed. The next day, he was given more penicillin, but vomiting and fever continued. On the morning of admission, his condition was unchanged and, in addition, his neck was stiff. A diagnosis of meningitis was made and he was sent to Sydenham Hospital.

Patient was well developed and nourished and weighed 10.4 kg. He was lethargic but did not appear to be critically ill. The temperature was 38.1°C. Neck was resistant to anterior flexion. Deep reflexes were equal but hyperactive. Abdominal reflexes were hyperactive. Babinski's reflex signs were negative.

Laboratory examination: Hgb. 5.5 gm./100 cc., WBC count of 13.32 thousand/cmm. with 56% leucocytes, 41% lymphocytes, and 3% monocytes. Urine analysis was negative except for a trace of acetone. Blood culture was negative. Lumbar puncture showed the cerebrospinal fluid to be cloudy with a white cell count of 3.48 thousand/cmm. with 98% leucocytes, a positive Pandy, and traces of sugar. The smear showed gram negative bacilli that quelled with type B. influenzal antiserum. Culture of the spinal fluid was positive for H. influenzae, type B. *In vitro,* the growth of this organism was inhibited by aureomycin 0.6 µgm./cc. broth.

On admission, the patient was given aureomycin 50 mg. intravenously and 125 mg. by mouth. Thereafter, he received a daily dosage of aureomycin 100 mg. intravenously for 6 days, and 500 mg.

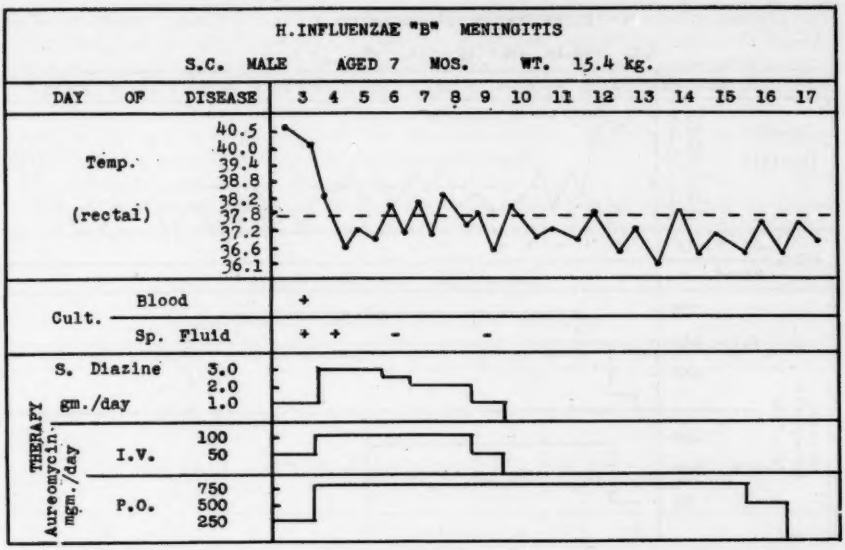

CHART 2

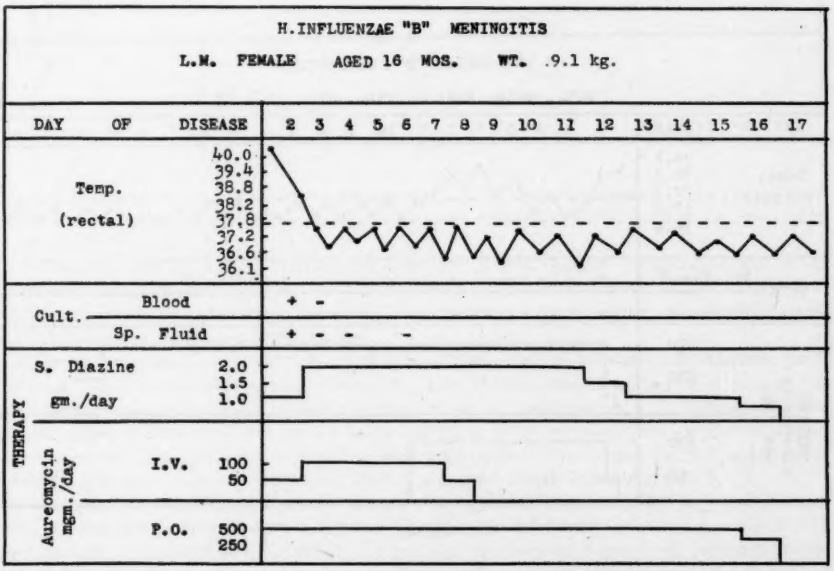

CHART 3

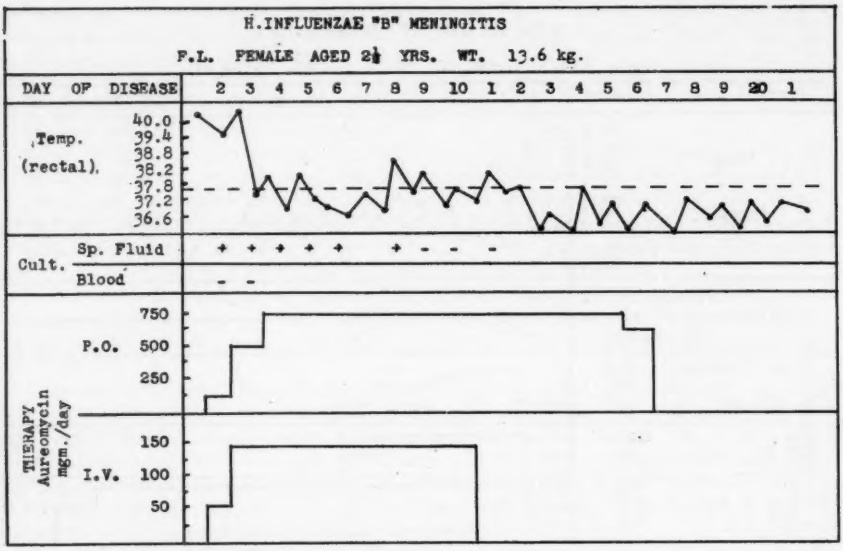

CHART 4

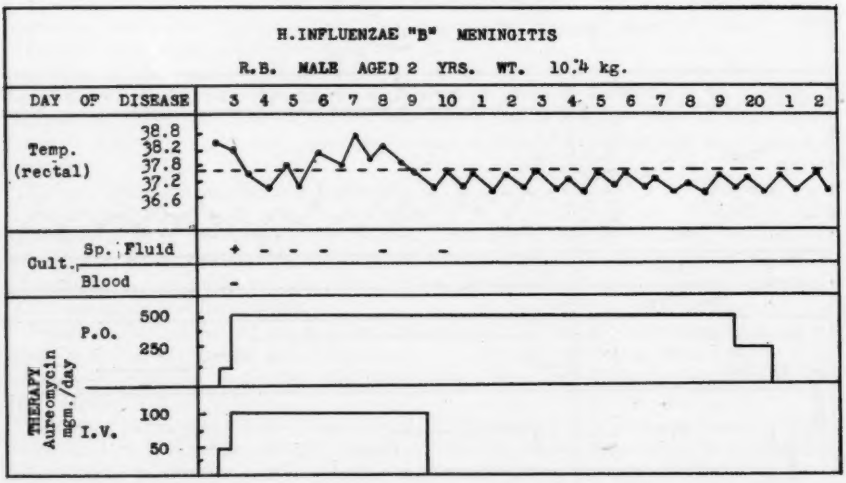

CHART 5

orally for 16 days, making a combined total dosage of 8.75 gm. On the day after therapy was instituted, cultures of the spinal fluid became negative and remained negative throughout the patient's course in the hospital. Temperature fell to normal within 24 hrs., but rose intermittently to 38.3° and 38.8°C. for the next 4 days. Thereafter, the patient remained afebrile and progressed rapidly to complete recovery. There were no evidences of drug toxicity at any time.

Case 5. E.W., a 6 yr. old Negro female, was transferred from the Harriet Lane Home Dispensary to Sydenham Hospital, with the diagnosis of influenzal meningitis.

Past and family histories were noncontributory.

Forty-eight hours before admission, she was seen by a physician because of vomiting and listlessness. Penicillin and sulfonamides were prescribed by mouth. On the day prior to admission, she

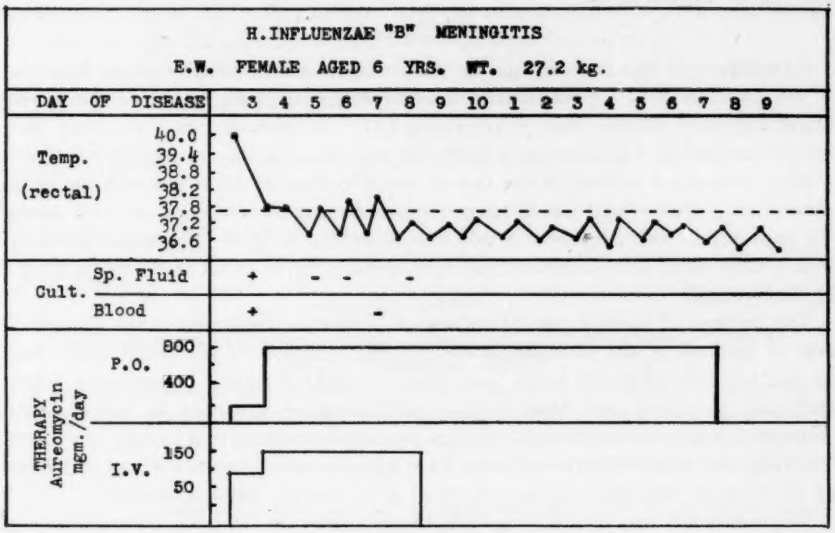

CHART 6

became irrational and ran a high fever. She was seen, on the day of admission, in the Harriet Lane Home Dispensary, where a diagnosis of H. influenzae meningitis was made. She was then transferred to Sydenham Hospital.

Patient was slender, asthenic and appeared acutely ill and sluggish. Temperature was 40°C. Eyes responded sluggishly to light. Neck was markedly resistant to flexion. Breath sounds were slightly suppressed over the entire right lung. Deep reflexes and the abdominal reflexes could not be elicited. Babinski's reflex signs were negative.

Laboratory examination: Hgb. 12.0 gm./100 cc., WBC count of 24 thousand/cmm. with 84% leucocytes, 12% lymphocytes and 4% monocytes. Urine analysis showed acetone to be present, but was otherwise negative. Blood culture was positive for H. influenzae, type B. Lumbar puncture showed spinal fluid to be cloudy with a white cell count of 24 thousand/cmm., a positive Pandy, and a complete absence of sugar. Smear showed gram negative bacilli that quelled with type B influenzal antiserum. Culture of the spinal fluid was positive for H. influenzae, type B.

On admission, the patient was given aureomycin 75 mg. intravenously and 200 mg. orally. Thereafter, she received a daily dosage of 150 mg. intravenously for 5 days and 800 mg. orally for 14 days, making a combined total dosage of 21.5 gm. On the day after therapy was instituted, spinal fluid cultures became negative and remained negative on further culturing. Blood culture taken on the 4th day after admission was negative. Temperature fell to normal within 24 hrs. and, except for a transient rise on the 4th day, remained normal throughout. Patient made a full recovery. There were no toxic drug reactions.

The findings on these 5 patients are summarized in Charts 2 to 6.

All 5 of these patients comprised the series treated at Sydenham Hospital. There was an additional patient with H. influenzae meningitis who was treated in the Harriet Lane Home with aureomycin and sulfadiazine in whom the outcome was fatal. This patient was a 4½ yr. old white male who was admitted to the hospital in a moribund condition after an illness of only 13 hrs.' duration. He was given aureomycin 75 mg. intravenously every 12 hrs. and aureomycin 250 mg. by rectum every 6 hrs. together with large doses of sulfadiazine intravenously and subcutaneously. In spite of this therapy, patient never regained consciousness and died 36 hrs. after admission. Spinal fluid cultures of the initial lumbar puncture and one performed 24 hrs. after admission were positive for H. influenzae, type B, but the postmortem spinal fluid culture was sterile. The postmortem blood culture was also sterile.

Discussion

Aureomycin, in doses of 20 mg./kg. body weight, was as effective in the treatment of mice infected with a small number of organisms as streptomycin and dihydrostreptomycin and more effective than polymyxin or Q-19. In doses of 1 or 5 mg./kg. body weight, aureomycin was somewhat less effective than the other four antibiotics tested, with a small infecting inoculum. In the face of overwhelming infection and with the initial dose of drug administered a short time prior to infection, there were no survivors among the mice treated with streptomycin, dihydrostreptomycin or Q-19. Aureomycin and polymyxin alone saved 25 and 40% of the mice, respectively, in doses of 20 mg. of drug / kg. body weight.

The response of the first two infants with H. influenzae meningitis to the administration of aureomycin and sulfadiazine was excellent. Cultures of the cerebrospinal fluid became negative within 48 hours, and there was striking clinical improvement within that same period of time. Both patients made complete recoveries. In both patients, aureomycin was given intravenously for six days and by mouth for an average of 14 days. The drug was well tolerated and there were no toxic manifestations. No exacerbations of fever or of meningeal signs were noted after therapy was discontinued.

The response of the three children treated with aureomycin alone was quite satisfactory, but not so impressive as that of the infants treated with both aureomycin and sulfadiazine. Patient 3 continued to have positive spinal fluid cultures for six days after therapy was instituted, in spite of the fact that aureomycin was demonstrable in the spinal fluid and that the organism had not become resistant to the antibiotic. Patient 4 showed symptomatic improvement and had negative spinal fluid cultures within 24 hours after admission, but he did not become completely afebrile until four days later. Patient 5 had negative spinal fluid cultures within 24 hours and, except for a transient rise of temperature on the fourth day, was afebrile throughout her stay in the hospital. Except for transient vomiting in the case of Patient 3, there were no toxic drug manifestations in these three patients. No exacerbations of fever or of meningeal signs were noted after therapy was discontinued. To date, there has been no evidence of residual brain or nerve damage in any of these patients.

In vitro determinations of the level of aureomycin in the cerebrospinal fluid indicated traces present in the spinal fluid of Patient 1, from 0.1 to 0.4 μgm./cc. in that of Patient 3, none in that of Patient 4, and traces in that of Patient 5. Studies on the spinal fluid of Patient 2 were not done.

One patient treated at another hospital but included in this series must be considered as having failed to respond to aureomycin and sulfadiazine therapy. This patient, moribund on admission, died 36 hours after admission, in spite of adequate treatment with both agents.

In this small series of cases, the case fatality was 16.6%.

SUMMARY

Aureomycin, in doses of 20 mg. / kg. body weight, was as effective in the treatment of mice infected with H. influenzae, type B, as streptomycin and dihydrostreptomycin, and more effective than polymyxin or Q-19.

Two infants with H. influenzae, type B, meningitis were treated successfully with aureomycin and sulfadiazine. Spinal fluid cultures became negative and marked clinical improvement occurred within 48 hours. Both patients went on to complete recovery. Three children were treated with aureomycin alone. Although their response to treatment was not so rapid as that of the infants treated with aureomycin and sulfadiazine, recovery was assured within four to seven days and subsequently there were no evidences of residual damage. No serious toxic reactions to aureomycin were apparent.

A sixth patient, desperately ill on admission, succumbed within 36 hours in spite of adequate treatment with combined aureomycin and sulfadiazine.

REFERENCES

1. Chandler, Caroline A., and Bliss, E. A., *In vitro* studies with aureomycin, Ann. New York Acad. Sc. **51**:221, 1948.
2. Bliss, E. A., and Chandler, Caroline A., *In vitro* studies of aureomycin, new antibiotic agent, Proc. Soc. Exper. Biol. & Med. **69**:467, 1948.
3. Bryer, M. S., and others, Aureomycin: Experimental and clinical investigations, J. A. M. A. **138**: 117, 1948.

SPANISH ABSTRACT

Aureomicina en el Tratamiento de Infecciones Experimentales y Clínicas con H. Influenzae, Tipo B

La actividad antibacterial de la aureomicina fué comparada con la activad de 4 otros antibióticos —estreptomicina, dihidrostreptomicina, polimixina y circulina (Q-19)—contra H. influenzae, tipo B. *In vitro,* se encontró que la aureomicina es inhibirotio a un nivel de 0.625 µgm./cc. caldo, la estreptomicina a 1.25 µgm./cc., la dihidrostreptomicina a 2.5 µgm./cc., la polimixina a 0.625 µgm./cc., y la circulina (Q-19) a 1.25 µgm./cc.

En ratones infectados intraperitonealmente con suspensiones mucina de H. influenzae, tipo B, la aureomicina fué tan eficaz como la estreptomicina, la dihidrostreptomicina y Q-19 en dosis de 20 mg./kg. peso de cuerpo cuando administrada subcutaneamente a 0, 5 y 23 horas después de la infección. Con este plan de dosis, la proporción de supervivencia para la polimixina y Q-19 fueron 85% y 63% respectivamente. Cuando la dosis original de la droga fué dada de 1 a 2 horas antes de la infección y las dos dosis subsecuentes fueron dadas de nuevo de 5 a 23 horas después de la infección, 25% de los ratones que recibieron aureomicina 20 mg./kg. quedaron vivos, mientras que ninguno quedó vivo después del tratamiento con estreptomicina, dihidrostreptomicina o Q-19.

A causa de estos resultados experimentales sugestivos y a causa de que se ha encontrado de que la aureomicina no produce esencialmente síntomas tóxicos en el hombre, se recomienda el tratamiento para pacientes con H. influenzae, tipo B. Dos pacientes con H. influenzae, tipo B, meningitis han sido tratados con aureomicina y sulfadiazina, y 3 han sido tratados con aureomicina sola. Los dos primeros pacientes recibieron aureomicina intravenosamente y oralmente en una dosis total combinada de 50 mg./kg. de peso de cuerpo. La dosis de sulfadiazina fué 0.1 mg./kg. peso de cuerpo. En ambos pacientes, la temperatura bajó de cerca de 40.5 a normal dentro de 24 horas, los cultivos del fluído espinal se volvieron estériles dentro de 28 horas y accompañadamente hubo una mejoría clínica notable con la desaparición de los signos meníngeos. Ambos pacientes vonvalescieron rapidamente y se restablecieron.

Se trataron tres pacientes con H. influenza meningitis con aureomicina sola en dosis de 50 a 100 mg./kg. peso de cuerpo. A pesar de que su respuesta al tratamiento no fué tan rápida como la de los pacientes tratados con aureomicina y sulfadiazina, el restablecimiento fué asegurado dentro de 4 a 7 días y subsecuentemente no hubo seña de cerebro restante o de perjuicio de nervios. No se encontraron serias reacciones tóxicas a la aureomicina.

Un sexto paciente, gravemente enfermo cuando se admitió, sucumbió dentro de 36 horas a pesar del tratamiento adecuado con aureomicina y sulfadiazina combinadas.

Sydenham Hospital

CLINICAL OBSERVATIONS ON THE USE OF AUREOMYCIN IN VARICELLA

By MILTON M. MAZURSKY, M.D., LYDIA WRIGHT, M.D., AND MANFRED WEICHSEL, M.D.
New York City

SINCE its introduction by Duggar[1] in 1948, aureomycin has been shown to be an effective agent in a number of rickettsial, bacterial and viral infections of man.[2-9] In 1933, Amies[10] established varicella as a specific viral disease when he obtained the elementary bodies of varicella in pure suspension and agglutinated them with the serum of patients convalescent from the disease.

Stimson[11] states that the vast majority of cases of varicella follow their normal course without complications; that in the average case a prompt recovery may be safely predicted within two weeks and that uncomplicated varicella is never fatal. However, it is to be noted that the high communicability of the disease is responsible for the exclusion of patients with varicella from school and work during the period of infectivity which averages 7 to 10 days. Moreover, the social conditions in many areas warrant the hospitalization of these patients and the utilization of hospital beds and personnel that are needed for those with more serious illnesses. For these reasons, it seemed expedient to determine the efficacy of aureomycin in shortening the course of varicella.

METHODS

Eighty-two patients were selected who met the following criteria:

1. Ages were limited to between 6 mos. and 12 yrs.
2. The exanthem was of less than 24 hrs.' duration.
3. None of the lesions were in the crust or scab stage on admission.

Cases were numbered consecutively as admitted regardless of age, color, sex or extent of involvement. The odd numbered cases served as controls, the even numbered ones received aureomycin. This resulted in there being 41 control cases and 41 cases treated with aureomycin.

The first dose of aureomycin was given immediately on admission and succeeding doses were given at 12 hr. intervals for a period of 72 hrs. During the 1st 24 hrs. the patients received a total of 50 mg./kg. body wt., and for each of the succeeding 24 hr. periods they received a total of 25 mg./kg. body wt. The medication was given orally.

No patient received any of the sulfonamides, penicillin, streptomycin, aspirin, alcohol sponges, tepid sponges, antipruritics or antihistaminics or was vaccinated, except for 1 case in which penicillin was given for a complicating right lower lobe pneumonia.

Each patient was examined by one of the authors on admission and by the same author on the following mornings at 24 hr. intervals for 6 examinations. In addition to the routine physical examination each day, special note was taken of the stages, extent and distribution of the lesions; the temperature range; and the presence or absence of an enanthem, complications or adenopathy.

RESULTS

Results shown in Table I indicate that aureomycin does not shorten the number of days in which new crops of varicella lesions appear as determined by the last day on

From Willard Parker Hospital, New York, N.Y.

Aureomycin used in this project was kindly supplied by Lederle Laboratories Division of the American Cyanamid Co., New York, N.Y.

(Received for publication May 19, 1949.)

TABLE I

SKIN LESIONS IN AUREOMYCIN TREATED AND CONTROL CASES

	First Day on Which All Lesions were Scabbed					Last Day on Which Macules, Papules or Vesicles were Noted					
Hospital Day	3rd	4th	5th	6th	6–10th	1st	2nd	3rd	4th	5th	6th
Aureomycin Cases	3	4	9	10	15	0	10	14	11	6	0
Controls	1	14	6	7	13	2	13	14	11	1	0

which macules, papules or vesicles were noted. Nor does the drug shorten the period of infectivity, as measured by the first day on which all the lesions were scabbed.

Aureomycin did not prevent the appearance of an enanthem where one was absent on admission, nor did it inhibit the appearance of fresh lesions in those cases already having an enanthem when hospitalized. It is interesting to note from Table II that 17 of the aureomycin-treated cases and 15 of the control cases developed enanthem lesions within 72 hours after admission.

In spite of aureomycin, there were still 25 out of 41 treated cases as compared to 29 out of 41 control cases whose temperatures had not returned to normal after 72 hours (Table III). The difference is statistically insignificant.

In both control and treated groups there were few and comparable complications appearing after hospitalization (Table IV). These along with the complications present on admission showed rapid resolution in both groups.

With a few exceptions, most cases in the control and treated groups showed a diffuse, generalized adenopathy on admission. By the end of the sixth hospital day, the adenopathy had remained essentially unchanged in all patients.

TABLE II

ENANTHEM IN AUREOMYCIN TREATED AND CONTROL CASES

	Enanthem Present on Admission. New Lesions Within 72 hrs.	Enanthem Present on Admission. No New Lesions Within 72 hrs.	Enanthem Absent on Admission. Lesions Appearing Within 72 hrs.	Enanthem Absent. No Lesions Appearing Within 72 hrs.
Aureomycin Cases	4	4	13	20
Controls	6	3	9	23

TABLE III

HOSPITAL DAY IN WHICH TEMPERATURES FELL AND REMAINED BELOW 37.6° C.

Hospital Day	1st	2nd	3rd	4th	5th	6th	6–10th
Aureomycin Cases	3	6	7	3	7	12	3
Controls	3	6	3	9	6	11	3

TABLE IV

INCIDENCE OF COMPLICATIONS IN AUREOMYCIN TREATED AND CONTROL CASES

AUREOMYCIN CASES		CONTROLS	
Complications present on admission	Complications developing during hospitalization	Complications present on admission	Complications developing during hospitalization
3 cases acute bilateral catarrhal otitis media	1 case acute tonsillitis	1 case pharyngitis	1 case cellulitis of R. orbital region secondary to infected lesion.
1 case acute R. catarrhal otitis media	1 case pharyngitis	1 case bilateral acute catarrhal otitis media and acute tonsillitis.	1 case acute pharyngitis.
1 case balanitis	1 case RUL pneumonia developing 7th day after admission.*	1 case acute tonsillitis.	1 case acute pharyngitis and tonsillitis.
2 cases acute tonsillitis and pharyngitis.		1 case acute bilateral catarrhal otitis media.	1 case RLL pneumonia developing 4th day after admission.
1 case acute tonsillitis and pharyngitis with purulent discharge from R. eye.		1 case R. acute catarrhal otitis media.	

* 4 days after aureomycin discontinued.

COMMENT

Aureomycin is of no use in the treatment of varicella. When compared to the same number of control cases, its trial use in 41 cases showed definitely that the drug did not shorten the course of the disease. Also, temperature elevations continued despite aureomycin; the drug did not prevent minor complications from occurring; nor did it hasten the disappearance of generalized adenopathy.

It was surprising to find that 20 of the 82 observed cases of varicella (an incidence of 24.4%) showed complications ranging from an acute pharyngitis to lobar pneumonias. This was a much higher incidence than was expected.

Two of the aureomycin-treated patients with a known exposure to epidemic parotitis one week prior to hospitalization developed parotitis on the 14th and 15th day, respectively, after admission—the 11th and 12th day, respectively, after the completion of their course of aureomycin. This would seem to indicate that aureomycin given during the incubation period of parotitis will not prevent the onset of the disease.

SUMMARY

Eighty-two patients with varicella between the ages of 6 months and 12 years whose rash was of less than 24 hours' duration and none of whose lesions were in the crust or scab stage were seen on admission and followed daily for six days. Forty-one of these patients received aureomycin orally (50 mg./kg. body weight the first 24 hours; 25 mg./kg. body weight the next 48). Forty-one cases served as controls.

Aureomycin had no effect on the cases treated.

Two patients developed epidemic parotitis despite the administration of aureomycin early in their incubation periods.

REFERENCES

1. Duggar, B. M., Introductory paper in Conference on Aureomycin—New Antibiotic, Section on Biology, New York Academy of Sciences, July 21, 1948.
2. Wright, L. T., and others, Treatment of lymphogranuloma venereum and lymphogranuloma inguinâle in humans, in Conference on Aureomycin—New Antibiotic, Section on Biology, New York Academy of Sciences, July 21, 1948.
3. Finland, M., Collins, H. S., and Paine, T. F., Use of aureomycin in human infections, in Conference on Aureomycin—New Antibiotic, Section on Biology, New York Academy of Sciences, July 21, 1948.
4. Schoenbach, E. B., and Boyer, M. S., Treatment of primary atypical nonbacterial pneumonia with aureomycin, J.A.M.A. **139**:275, 1949.
5. Finland, M., Collins, H. S., and Paine, T. F., Aureomycin: New Antibiotic, J.A.M.A. **138**:946, 1948.
6. Spink, W. W., Braude, A. I., Castaneda, M. R., and Goytia, R. S., Aureomycin therapy in human brucellosis due to brucella melitensis, J.A.M.A. **138**:1145, 1948.
7. Cooke, C., Rocky Mountain spotted fever treated with aureomycin, J.A.M.A. **138**:885, 1948.
8. Ross, S., and others, Aureomycin therapy of Rocky Mountain spotted fever, J.A.M.A. **138**:1213, 1948.
9. Woodward, T. E., and others, Aureomycin in treatment of experimental and human tularemia, J.A.M.A. **139**:930, 1949.
10. Amies, C. R., Elementary bodies of varicella and their agglutination in pure suspension by serum of chickenpox, Lancet **1**:1015, 1933.
11. Stimson, P. M., Manual of Common Contagious Disease, ed. 4, Philadelphia, Lea & Febiger, 1947, p. 278.

SPANISH ABSTRACT

Observaciones Clínicas en el Uso de la Aureomicina en La Varicela

Ochenta y dos pacientes con varicela entre las edades de 6 meses y 12 años, cuyo salpullido era de menos de 24 horas de duración y ninguna de las lesiones estaban en el estado de costra fueron vistos al admitirse y se siguieron diariamente por seis días. Cuarenta y uno de estos pacientes recibieron aureomicina oralmente (50 mg./kg. peso de cuerpo las primeras 24 horas; 25 mg./kg. peso de cuerpo las siguientes 48 horas). Cuarenta y un caso sirvieron como controles. La aureomicina no tuvo efecto en los casos tratados. Dos pacientes desarrollaron parotitis epidémica a pesar de la administración de aureomicina en su período de incubación.

Children's Hospital, Buchtel Avenue at
Bowery Street, Akron, Ohio

CHEMOTHERAPY OF TUBERCULOSIS IN CHILDREN

By EDITH M. LINCOLN, M.D., AND THOMAS W. KIRMSE, M.D
New York City

RECENT advances in chemotherapy have stimulated great interest in the treatment of tuberculosis in children. Streptomycin is undoubtedly the most effective of the tuberculostatic agents. With its use, remarkable therapeutic results have been achieved. Various sulfones such as diasone®, promin®, sulphetrone® and promizole® have also been shown to possess definite bacteriostatic action in clinical trials. Other drugs such as para-aminosalicylic acid (PAS) are on trial but their place in the treatment of clinical tuberculosis is not established.

Chemotherapy of tuberculosis in the Chest Clinic of the Children's Medical Service of Bellevue Hospital began in 1944, with the use of promizole®. This drug had been shown by Feldman, Hinshaw and Mann[1] to cause marked retrogression of tuberculous lesions of hematogenous origin in guinea pigs. Five successive cases of meningitis were treated first; all the children died with no deviation from the usual course and duration of the disease. Postmortem examination of the brains of two of these cases showed no demonstrable effect of the drug. Treatment of miliary tuberculosis was then undertaken because it is also a form of tuberculosis with a high fatality rate and furnishes good clinical material for testing the value of a drug. Furthermore the average duration of acute miliary tuberculosis is more prolonged than that of tuberculous meningitis, thus allowing more time for the action of a drug.

Ten cases of generalized miliary tuberculosis have been treated with promizole® alone.[2-4] In three of these for various reasons treatment had to be discontinued after 12 to 26 days. The remaining seven cases were treated for longer periods of time; two of these children died 43 days and 4½ months after therapy was begun. The other five show complete recession of the miliary tubercles on roentgenogram and are well 2 to 4½ years after beginning treatment. Disappearance of miliary nodules on roentgenogram was used as objective evidence of therapeutic response to promizole®. Roentgen changes were not observed in any case until at least 10 weeks after promizole® was first given. Complete roentgenographic clearing did not occur in less than six months from the start of medication. Enough promizole® was given to maintain a blood level of 1 to 3 mg./100 cc. This effect was produced with a daily amount of promizole® varying from 1 to 4 gm., divided into four equal doses given orally every six hours. The decision to continue therapy for a long time was based on the reports of experimental work as well as on clinical experience with our first cases. Feldman and others[5] had shown that in animals apparently cured by sulfones, viable tubercle bacilli could be recovered from the spleen. Medlar and Sasano[6] reported relapses in apparently cured animals after

From the Chest Clinic of the Children's Medical Service, Bellevue Hospital, and the Department of Pediatrics, New York University, New York, N.Y.

Aided by grants from the Division of Research Grants and Fellowships of the National Institutes of Health, U. S. Public Health Service, The National Tuberculosis Association and Parke, Davis & Company.

Promizole® was supplied by Parke, Davis & Company.

(Received for publication May 1, 1949.)

cessation of treatment with promin®. Our children also showed continued evidence of active tuberculosis in the persistence of the primary focus on roentgenogram after the hematogenous lesions had disappeared. Moreover, in two of our patients, extra-pulmonary complications continued to develop while the miliary mottling on roentgenogram was clearing. In order to prolong bacteriostatic action it was decided to continue treating cases with promizole® after the miliary tuberculosis was apparently arrested and three years was arbitrarily decided on for the duration of therapy.

The immediate toxic effects of promizole® are vomiting and cyanosis. The former has been severe in only one case. Two of the first cases had transient leucopenia after three weeks and after four months of treatment. In all cases there was an enlargement of the thyroid gland within two to five months after the first administration of the drug. This goitrogenic effect is apparently similar to the action of thiourea and sulfonamides causing hyperplasia and hyperemia with increase in cell height and diminution of colloid. In one of the two failures to cure miliary tuberculosis with promizole®, post-mortem examination of the thyroid gland showed this characteristic change. The administration of desiccated thyroid gland in small amounts apparently counteracts this action of the drug and causes the thyroid to diminish in size. Another toxic reaction of promizole® which is not as constant as the goitrogenic one is the development of secondary sex characteristics. Enlarged nipples and pubic hair appeared in two of the girls when 3 and 6 years old. Assays of urinary 17-ketosteroids gave elevated values. One child developed roentgenographic evidence of an enlarged heart soon after her thyroid enlarged. The cardiac size returned to normal while the child was taking desiccated thyroid. This increase in the size of the cardiac shadow on roentgenographic examination may have been due to a cretinoid state produced by promizole®. A cherry-red or pink urine appears at some time in all patients receiving promizole®. Occasionally a substance is present in the urine which gives a reducing reaction with Benedict's solution.

The group of children with miliary tuberculosis treated with promizole® is small, but since five out of seven cases have survived more than two years with no recurrence of the miliary mottling on roentgenogram it is believed that promizole® must have an inhibitory effect on hematogenous tuberculosis in children similar to its effect on guinea pigs. Promizole® has the advantage of ease of administration and relatively little toxic action. It has the disadvantage of acting slowly and is, therefore, inadequate for the treatment of rapidly progressive cases of hematogenous tuberculosis.

Combined Therapy with Streptomycin and Promizole®

Streptomycin was first made available to the Chest Clinic of the Children's Medical Service of Bellevue Hospital in December 1946. It was obvious from reports in the medical literature that it was a therapeutic agent far superior to anything that had ever been used previously in tuberculosis. However streptomycin has two disadvantages: first, its selective toxicity for the VIII C nerve and especially the vestibular branch, symptoms of which appear regularly after administration of the drug for relatively short periods. There is evidence that the substitution of dihydrostreptomycin may modify this objection by markedly delaying or preventing this toxic effect. The second disadvantage is the frequent emergence of resistant tubercle bacilli after prolonged therapy. Partly because of these defects in streptomycin therapy and partly because we were impressed by the tuberculostatic effect of promizole®, it was decided to treat children with tuberculous

meningitis and miliary tuberculosis with a combination of the two drugs. The addition of another drug to streptomycin seemed logical. It was reasoned that the use of two different types of therapeutic agents might minimize the chances of developing drug resistance. Moreover, M. I. Smith and others[7] have shown that the simultaneous use of a sulfone and streptomycin in guinea pigs produced therapeutic results beyond the simple summation of the effects of the two drugs. In order to get the maximum advantage of combining another agent with streptomycin the second drug should be one which by itself it known to affect favorably the course of tuberculosis. Definite evidence of the inhibitory action of promizole® in miliary tuberculosis had been obtained. Therefore, promizole® seemed a suitable drug to combine with streptomycin. It seemed desirable in the treatment of miliary tuberculosis and tuberculous meningitis to continue tuberculostatic action for long periods of time. Streptomycin, however, is unsuitable for prolonged therapy because of its potential toxicity and the tendency of the tubercle bacillus to become resistant to it. By the simultaneous use of streptomycin and promizole® advantage could be taken of the rapid action of streptomycin; therapy could then be continued with the sulfone which can be given safely and effectively for years.

Treatment of Miliary Tuberculosis with Streptomycin and Promizole®

Ten children with miliary tuberculosis were treated by combined therapy. A summary of the cases is shown in Table I. All but one of the cases received streptomycin 1 gm. intramuscularly daily for 120 days; Case 4 received only 0.4 gm. daily. All cases received promizole® orally 4 times daily in amounts sufficient to secure a blood level of 1 to 3 mg./100 cc. It is planned to continue the administration of promizole® for 3 yrs.

One patient died 6 days after therapy was begun; a 2nd patient, after recovery from miliary tuberculosis, died of tuberculous meningitis. The remaining 8 cases remain well 6 to 23 mos. later.

The rate of clearing of the miliary mottling on roentgenographic examination was much faster

TABLE I

Miliary Tuberculosis Treated with Streptomycin and Promizole®

Data as of March 1, 1949

Case	Sex	Age at Time of Diagnosis	Interval Diagnosis to Clearing	Results	Development of Meningitis	Other Complications	Comments
1. H.R.	M	11 yrs.	7 wks.	Good condition 23 mos. later.	1 wk.	Tbc. of spine. Tbc. of ulna.	Case 2 of meningitis series.
2. J.Y.	M	4 yrs.	7 wks.	Died 11 mos. later of meningitis.	1st episode 12 wks. Relapse 19 wks. later.	0	Case 3 of meningitis series.
3. O.V.	F	5 yrs.	10 wks.	Well 15 mos. later.	0	Thrombopenic purpura.	
4. W.C.	M	9 mos.	8 wks.	Well 14 mos. later.	0	Endobronchial Tbc. with collapse RML.	
5 A.M.	F	8 mos.	18 wks.	Well 14 mos. later.	On admission.	0	Case 9 of meningitis series.
6. G.G.	F	8 mos.	8 wks.	Well 11 mos. later.	0	0	
7. P.N.	M	6 mos.	—	Died after 6 days.	0	0	
8. R.Co.	M	13 mos.	12 wks.	Well 10 mos. later.	6 wks.	0	Case 11 of meningitis series.
9. C.R.	F	23 mos.	6 wks.	Well 6 mos. later.	0	Endobronchial Tbc. with collapse RML.	
10. R.A.	M	20 mos.	8 wks.	Well 6 mos. later.	0	0	

TABLE II

18 MENINGITIS PATIENTS TREATED WITH STREPTOMYCIN AND PROMIZOLE®

Data as of March 1, 1949

Case	Age at Onset	Chest Roentgenogram and Other Evidences of Tbc.	No. Days Treated	Total gm. Streptomycin	Maximum Daily Dose of Promizole®	Results
1. E.S.	9 mos.	Primary	66	42.0	1.5	Hydrocephalus on admission. *Died* 66th day of treatment.
2 H.R.	11 yrs.	Miliary; Spondylitis	183	278.0	6.0	Spinal fusion after recovery. Well 23 mos. after meningitis.
3. J.Y.	4 yrs.	Miliary	176 109	229.0 163.0	4.0 4.0	*Died* during relapse 11 mos. after onset of miliary.
4. L.W.	3 yrs.	Primary	191	207.0	2.0	Well 22 mos. after meningitis.
5. E.D.	2 yrs.	Primary	188	106.0	6.0	Well 21 mos. after meningitis.
6. S.E.	6 yrs.	Primary	201	249.0	4.0	Well 20 mos. after meningitis.
7. O.V.	23 mos.	Primary	183	186.0	6.0	Well 18 mos. after meningitis.
8. B.P.	3 yrs.	Calcified Primary	182 180 39	319.0 183.0 41.0	4.0 8.0 8.0	1st relapse 43 days, 2nd relapse 44 days after completing previous courses of treatment. Spastic paralysis R. arm; deaf. Doing well 2 mos. after 2nd relapse. 16 mo. follow-up.
9. A.M.	8 mos.	Miliary	203	199.0	4.0	Spastic paralysis R. arm. Otherwise well 14 mos. after meningitis.
10. M.M.	5 yrs.	Calcified Primary	180 180	246.0 185.9	4.0 8.0	Relapsed 45 days after completing treatment. Atrophy L. leg with foot drop; 14 mos. since onset.
11. R.Co.	13 mos.	Miliary	222	140.0	4.0	Good condition 9 mos. after onset.
12. M.P.	6 yrs.	Calcified Primary	180	184.0	6.0	Excellent condition 9 mos. after onset.
13. G.V.	10 mos.	Primary	10	11.0	2.0	*Died* 10th day of treatment.
14. M.G.	11 mos.	Primary	18	17.0	2.0	*Died* 18th day of treatment.
15. V.O.	15 mos.	Primary	180	182.1	6.0	Good condition 8 mos. after onset.
16. M.K.	5 yrs.	Calcified Primary	180	184.0	4.0	Good condition 7 mos. after onset.
17. C.M.	13 mos.	Primary	39	34.5	2.0	*Died* 39th day of treatment—exfoliative dermatitis.
18. W.M.	2 yrs.	Calcified Primary	140	142.4	6.0	Doing well 5 mos. after onset. Still under treatment.

with combined therapy than with promizole® alone, an average of 9 wks. as compared to 8 mos. Relapse of miliary tuberculosis has not occurred either in patients treated with promizole® alone or combined with streptomycin.

TREATMENT OF TUBERCULOUS MENINGITIS WITH STREPTOMYCIN AND PROMIZOLE®

Eighteen cases of tuberculous meningitis have been treated; 13 survive, 8 of them for more than a year. The most encouraging finding is that so far the general behavior of all the survivors is well within normal limits; only 4 have physical handicaps and none of these are severe. A summary of the cases treated is shown in Table II.

Streptomycin was given intramuscularly in the first cases in dosage of 0.5 to 2 gm. daily depending on the age and size of the child, but no attempt was made to give the drug on a weight basis. In the more recent cases dosages have not exceeded 1 gm. daily. This is usually given twice

daily; 0.5 gm., at 8 a.m. and again at 4 p.m. A single daily dose can be given comfortably to large or well nourished children. Streptomycin given intramuscularly is continued for 180 days. In addition, 0.1 gm. is given once daily by the intrathecal route until toxic symptoms or mechanical difficulties occur. Thereafter this amount is given every 2 days but if toxic symptoms again occur, 0.05 gm., every 2 or 3 days, is given until a series of 40 treatments has been completed.

Promizole® is given orally at 6 hr. intervals. The initial dose of 1.0 gm. daily is given for several days. In the absence of signs of toxicity, a gradual step-like increase from 1.0 to 2.0 gm. or higher is then made every few days or weekly until therapeutic blood levels (1.0 to 3.0 mg./100 cc.) are obtained. Treatment with promizole® is continued for 3 yrs. In the event of relapse, the full course of streptomycin is repeated by both intramuscular and intrathecal routes.

Toxic Reactions

Although the general plan of treatment was the same in each case, individual variations due to toxic reactions sometimes required interruption of treatment for several days or weeks. There is apparently less toxic reaction to promizole® when it is given in combination with streptomycin. Some degree of cyanosis is seen in the majority of cases. The goitrogenic action of the drug is still apparent; enlargement of the thyroid gland tends to be less marked, but an elevation in the cholesterol content of the blood is usually present. One 6 yr. old girl (meningitis case 6) has shown development of nipples and breast enlargement after 8 mos. of therapy. No leucopenia was noted in the children under combined therapy although the dose of promizole® necessary to obtain a blood level of 1 to 3 mg./100 cc. was much higher than when promizole® was used alone. A cherry-red or pink urine continues to appear at some time in all patients receiving promizole® even when combined with streptomycin.

The toxic reactions to streptomycin have been similar to those reported elsewhere. Vomiting was frequent and in 1 patient was so severe that therapy had to be temporarily discontinued. Four children had generalized papular or urticarial eruptions, in 2 cases associated with or followed by eosinophilia. One patient developed exfoliative dermatitis (meningitis case 17). One child showed temporary elevation of the nonprotein nitrogen content of the blood associated with cylindruria. The most constant reaction was ataxia. Every patient showed some degree of unsteadiness after 3 or 4 wks. of treatment. Clinically, every child who recovered has made an apparently adequate adjustment to any damage that may have been sustained by the vestibular branch of the VIII C nerve. They all play and run like normal children. Recently, for the first time, it has been possible to secure satisfactory caloric stimulation tests (Kobrak) even on the youngest cases and it has been found that response to stimulation is usually lost, sometimes as early as the 2nd wk. of therapy.

Following intrathecal administration of streptomycin, increased vertigo, ataxia, transient nystagmus and strabismus as well as projectile vomiting may develop within 1 to 4 hrs. Occasionally opisthotonus, convulsions, muscle rigidity or sudden high temperature may occur. Following these more severe reactions, the patient may become drowsy and fall into a quiet sleep. On awakening there is usually full recovery from these alarming symptoms although complete loss of reflexes with muscle flaccidity may be present for 24 hrs. or more. It has been impossible to secure satisfactory audiograms in most of the cases and therefore possible damage to the hearing apparatus cannot be evaluated. One patient became blind and deaf during the first month of treatment with streptomycin. Vision and hearing were ultimately completely restored. Two other patients with meningitis have become deaf while under treatment but one has shown marked improvement since the termination of streptomycin therapy. Since no instance of deafness has been seen except following meningitis, it is not known whether the deafness was caused by streptomycin or by meningitis.

Clinical Course of Tuberculous Meningitis in Cases Under Therapy

Even when streptomycin and promizole® are given early in the course of meningitis there is usually no immediate response. The course at first is usually that of an untreated patient. The child often develops the neurologic pattern of the 2nd stage of meningitis and under therapy this stage lasts from 2 wks. to several months. Even the 3rd or comatose stage of the disease may develop and yet be followed by complete recovery. Hemiplegia or paralysis of an extremity may be transient, clearing before the end of therapy, or a moderate degree of spastic paralysis may persist. Such lesions in these children may continue to improve long after streptomycin therapy is completed. Evidence of cranial nerve involvement clears slowly. In one patient strabismus developing during the

first weeks of meningitis did not entirely disappear until 6 mos. after the onset. Diminished and even absent superficial and deep tendon reflexes persist in some cases until some time after streptomycin therapy is concluded. Fever declines slowly and often persists for several months. Frequently gain in weight and lessened weakness are noted during the second month of therapy. A few of the recovered cases seemed entirely well even before intramuscular streptomycin was discontinued. In many cases convalescence was prolonged beyond the 6 mos.' period of combined therapy. The general behavior of the survivors seems within normal limits but only time will tell whether the cortical damage these children probably sustained has been completely repaired. EEG of the recovered cases have been normal with 3 exceptions which showed unilateral brain damage.

Blood and Cerebrospinal Fluid

Promizole® blood and spinal fluid levels show great variation. Following single oral doses of promizole®, maximum blood levels are obtained in 2 to 4 hrs. There is no apparent relation between the dosage, the weight of the child and the levels. It has been interesting to note that children of the run-about age group (2 to 5 yrs.) will frequently attain high levels with small doses (0.5 to 2.0 gm. daily) while infants and older children may require 4 to 8 gm. daily to attain therapeutic levels. Since unnecessarily high levels may result in symptoms of toxicity, it is undesirable to attempt to regulate the dose of promizole® by the weight of the patient. Some patients will at times reach equivalent values in blood and spinal fluid; more often the spinal fluid level is only a fraction of that obtained in the blood. Promizole levels are not influenced by the presence or absence of meningitis.

The authors' experience with streptomycin levels in a small series of patients is incomplete. However, sufficient evidence has been collected to indicate that as the disease subsides there is a tendency for the concentration in the spinal fluid to decline while the blood level may remain stationary. With clinical improvement several patients in this series who were still receiving streptomycin intramuscularly have shown a decline to zero in the level of streptomycin in the spinal fluid. Spinal fluid levels of streptomycin (Price method) less than 1 μg./cc. were repeatedly obtained in 5 patients treated with streptomycin intramuscularly who at no time showed any clinical or laboratory evidence of meningitis. Streptomycin levels of 5 to 40 μg./cc. were obtained in 2 patients with miliary tuberculosis some time before a definite diagnosis of meningitis was established.

Protein content of the spinal fluid remained elevated in only 5 patients at the time all streptomycin had been completed; 2 of these relapsed. Cells varied greatly but returned to normal in all survivors before intramuscular streptomycin had been completed. Chlorides declined too slowly and too late in the disease to be of diagnostic or prognostic significance. Spinal fluid sugar values were normal in 4 of the 18 cases at the time meningitis was diagnosed. Three of these were cases of miliary tuberculosis and 2 of them had already been started on intramuscular streptomycin. This masking of the diagnosis of meningitis in cases of miliary tuberculosis by normal spinal fluid sugar content has led to a search for other tests by which early diagnosis can be accomplished. In addition to streptomycin levels, the Levinson test and colloidal gold curves may be helpful aids as well as possible indices to prognosis or temporary arrest of the disease process. Such aids may be of particular importance in the early recognition of relapse. In the 3 patients who relapsed, the diagnosis was made by spinal fluid changes before any clinical evidence of meningitis was apparent. In the absence of meningitis, the Levinson test was negative and the colloidal gold curve normal. The trend of these 3 tests, streptomycin levels, Levinson and colloidal gold, may ultimately provide some help in determining the duration of therapy.

Tubercle bacilli fully sensitive to streptomycin were recovered, from the spinal fluid of the 3 cases of tuberculous meningitis who relapsed after 6 mos.' treatment with combined therapy. In 1 of these patients (meningitis case 3) after 2 mos. of further intrathecal therapy, tubercle bacilli were obtained on culture of the spinal fluid which were resistant to streptomycin and the patient thereafter developed clinical meningitis and died. Tubercle bacilli had been cultured from the blood of this boy during his initial illness of miliary tuberculosis 9 days after the institution of intramuscular streptomycin. It is known that with a large population of bacilli, organisms resistant to a drug are more likely to emerge. The 2 other cases who relapsed showed no diminution of sensitivity to streptomycin and successfully completed the period of 6 mos.' retreatment with streptomycin. One of these children (Case 8) subsequently relapsed a 2nd time and again tubercle bacilli fully sensitive to streptomycin were recovered from the spinal fluid.

Treatment of Other Forms of Tuberculosis

In addition to the cases of miliary tuberculosis and meningitis treated with combined therapy, children with other forms of tuberculosis have been treated with streptomycin as the sole chemotherapeutic agent. Because of the disadvantages of this antibiotic which have been cited before, treatment with streptomycin alone has been restricted to forms of tuberculosis which might be benefited or cured by a course of treatment not exceeding 6 wks.; in some of these cases temporary control of the disease permitted procedures such as surgery or collapse therapy, which would otherwise have been contraindicated.

In the first group of cases, if the anticipated response to streptomycin did not occur, treatment was occasionally prolonged to 90 or even 120 days. Some of the earliest cases also received a larger daily amount of streptomycin than is used at present. In forms of tuberculosis other than meningeal or miliary, streptomycin is now given only on a weight basis (Table III). Recently, as the advantages of combining another drug with streptomycin have become clearer, combined therapy has been used except where streptomycin is used for only a few days.

Certain lesions respond spectacularly to streptomycin. The authors have seen tuberculous laryngitis apparently cured after a few weeks of treatment. Marked symptomatic improvement has been seen in

TABLE III

Streptomycin Dosage on Weight Basis

Weight in Pounds	Gm. Intramuscularly daily
under 10	0.3
10–19	0.4
20–39	0.5
40–59	0.6
60–89	0.75
90 and over	1.0

2 children with ulcerative tuberculous enteritis after a short course of the antibiotic. Draining cutaneous sinuses closed promptly under therapy.

The results in treatment of endobronchial tuberculosis have been good but perhaps slower and less successful than has been reported for adults. Possibly the difference in response is due to the fact that the pathogenesis of endobronchial tuberculosis in adults and children frequently is different. Seventeen children have received streptomycin for endobronchial tuberculosis and the progress of the disease under treatment has been followed by bronchoscopy. In most instances the lesions have disappeared by the end of the therapy period of 6 wks. but in 3 cases, local progression of the disease occurred while under treatment.

Bronchogenic spread due to locally progressive primary tuberculosis has also been treated successfully (figs. 1 and 2). Before chemotherapy such cases would have had a grave prognosis. Six children under 3 yrs. of age have been treated; in 4 cases the tuberculous bronchopneumonia was bilateral, in 2 cases unilateral. All these children are alive and in good condition 8 to 24 mos. after treatment was started. In all there was rapid clinical improvement with disappearance of tubercle bacilli in the gastric contents and clearing of the bronchogenic spread.

Treatment of moderate to far-advanced pulmonary tuberculosis of the so-called reinfection type in children has also been attempted. Results have been similar to those reported for adults with initial rapid improvement in symptoms and marked diminution in the extent of exudative lesions. No cases have been seen in which the lesions resolved completely. Moreover, 3 of the 1st 6 cases treated with streptomycin alone relapsed several months after therapy was discontinued. This was probably due to the fact that the initial good response to treatment created undue optimism and pneumothorax was not considered early in the course of treatment. In later cases we have learned to use streptomycin as a valuable adjunct to pneumothorax and other accepted methods of treatment. In children whose initial roentgenograms contraindicated the use of collapse therapy, this form of treatment was given successfully after temporary control of the disease by streptomycin (fig. 3).

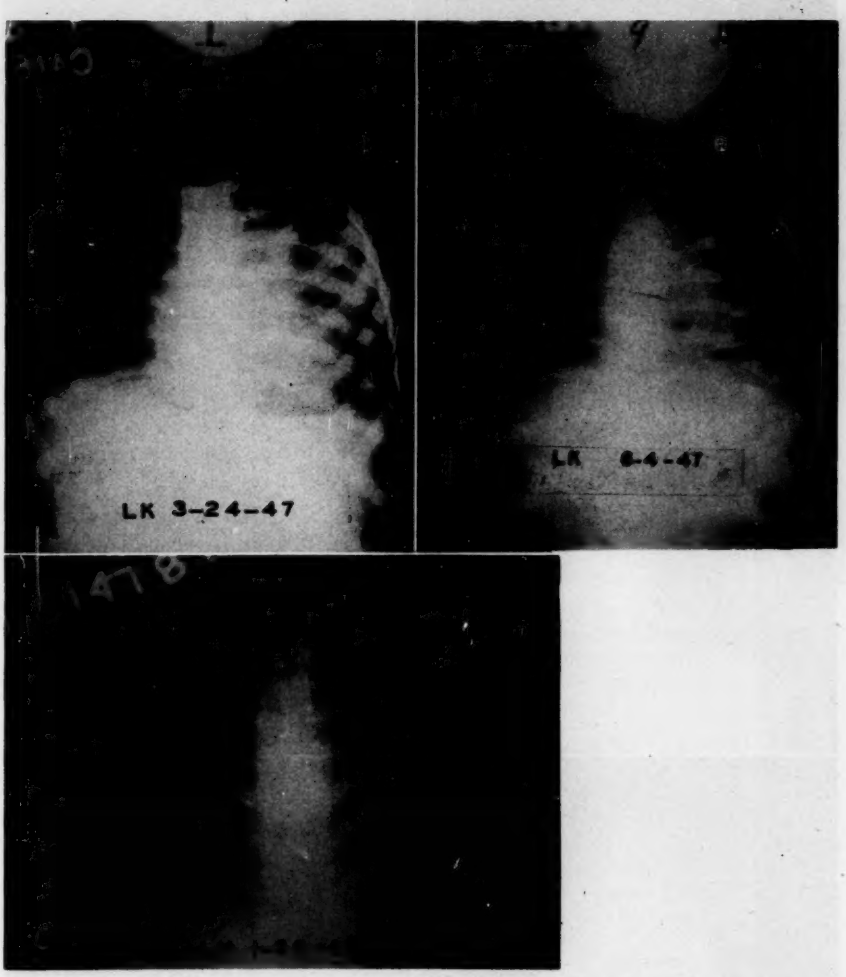

FIGURE 1

L. K., 3 yrs. old. A. Tuberculosis of LUL with cavitation and bronchogenic spread to the RUL. Culture of gastric washings positive for tubercle bacilli. B. 54 days after streptomycin therapy; clearing of RUL; cavity in LUL not visualized. Gastric washings negative for tubercle bacilli. Six months later recurrence of moist rales in LUL; sputum again positive for tubercle bacilli which show no loss of sensitivity to streptomycin. Re-treated with streptomycin and promizole®. C. 22 mos. after A showing persistence of primary focus in LUL with highlight still visible. Sputum negative; child in excellent general condition.

With a similar use of streptomycin, successful excision of masses of caseous tuberculous lymph nodes has been carried out in several instances without sinus formation (fig. 4) and many other surgical procedures including pneumonectomy have been made possible (fig. 5).

A great deal has been learned about the value and limitations of streptomycin by the observation of its effect on tuberculous foci other than those to which treatment was primarily directed. For example, in a few instances in which draining cutaneous sinuses were treated, apparent beneficial effect was observed in tuberculosis of the bone. A striking example was seen in a child with exten-

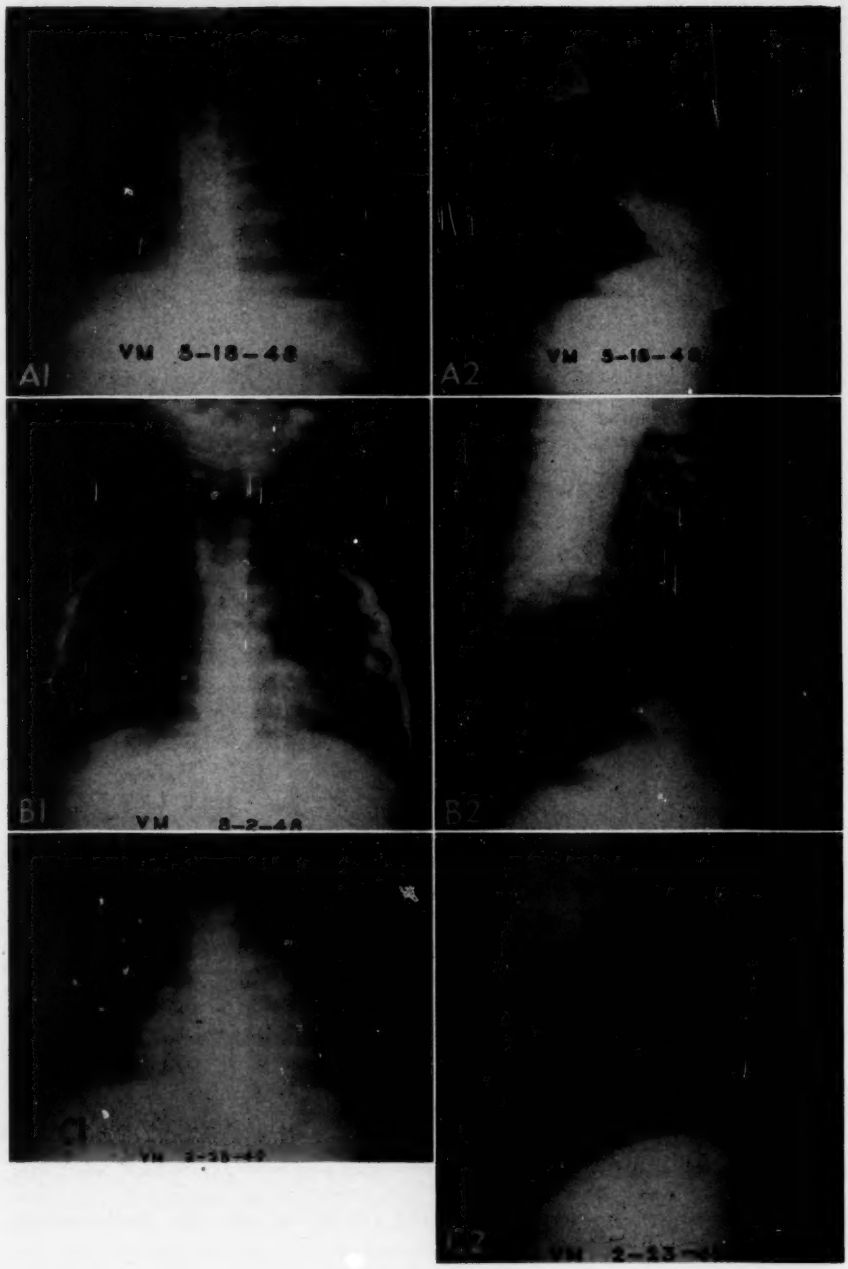

FIGURE 2

V. M., 17 mos. old, wt. 5.4 kg. A. Caseous and cavitating tuberculosis of L lung with bilateral bronchogenic spread; collapse of RML with emphysema RLL best seen in lateral view; culture of gastric washings positive for tubercle bacilli. B. After completion of treatment with streptomycin and promizole® (total 90 days) showing distended cavity and partial re-aeration of RML. Marked clinical improvement; wt. 8.6 kg. C. 9 mos. after beginning treatment showing widening of mediastinum to R and L with infiltration around L hilum, extending to base—interpreted as healing primary tuberculosis; cavity not visible. Wt. 12.7 kg.; excellent condition.

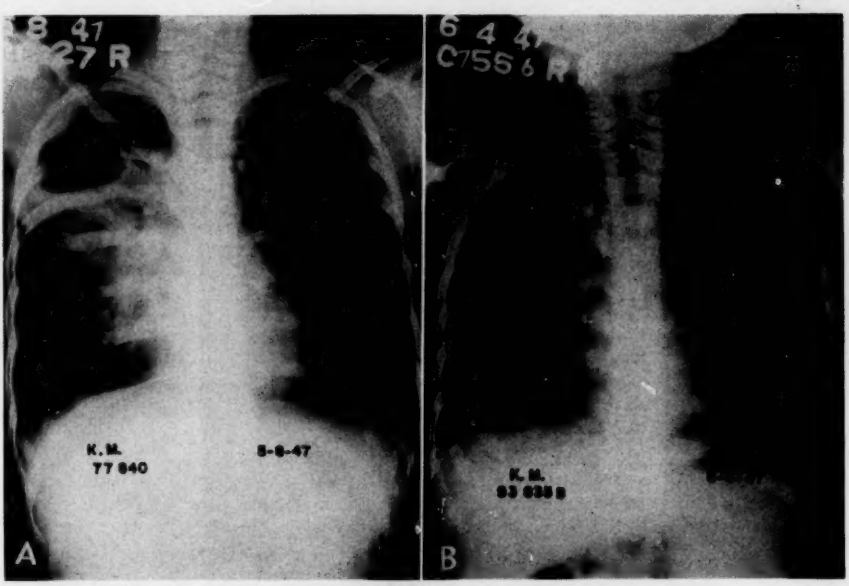

FIGURE 3

K. M., 8 yrs. old. Acutely ill, toxic, high fever; sputum markedly positive. A. bilateral cavitating tuberculosis more marked on R side. Pneumothorax contraindicated because of extent of exudative lesion. B. After 26 days of streptomycin therapy showing marked clearing which permitted a successful pneumothorax on R side. Roentgenographic changes accompanied by clinical improvement, loss of fever, conversion of sputum.

sive destructive disease of the sacro-iliac joint. Under streptomycin therapy a large cold abscess with a draining sinus disappeared. In addition there was complete functional recovery with no remaining muscle spasm. The roentgenogram, however, while greatly improved, still showed pathologic changes. The authors have also observed a child 3 yrs. old whose miliary tuberculosis had been arrested by promizole®. Subsequently he developed a tuberculous epididymitis, a small but progressive lesion in the tibia and a tuberculous spondylitis. Under streptomycin therapy the testicle and roentgenographic appearance of the tibia returned to normal but the spondylitis progressed and a spinal fusion was later done.

During streptomycin treatment for other forms of tuberculosis the drainage from chronic tuberculous otitis media was usually temporarily diminished or suppressed but often recurred. No improvement of the accompanying mastoiditis was observed.

Primary tuberculosis has not been treated with streptomycin. However there has frequently been an opportunity to observe the response of a primary tuberculous complex to streptomycin therapy. In addition studies have been made of serial roentgenograms in patients first seen here after they had received streptomycin elsewhere for uncomplicated primary tuberculosis (fig. 6). No change in the roentgenographic appearance of the primary tuberculosis has been found beyond that expected in the normal course of the disease.

DISCUSSION

There is clinical evidence in all published series of cases of tuberculous meningitis that streptomycin has a definite and beneficial effect on the course of this disease. Moreover, Kidd[8] has provided evidence from pathologic studies that streptomycin causes healing of tuberculous cortical and meningeal foci. Reports from the Sick Children's Hospital in Paris,[9] the Medical Research Council in England[10] and the Veterans Administration, the Army and Navy in the United States[11] give fairly uniform survival rates of 36

to 37% six months after treatment had been started. More prolonged follow-up, however, has reduced the percentage of survivors.[12] Recently McDermott[13] stated that sustained and satisfactory recoveries may be obtained in 10 to 15% of meningitis cases treated with streptomycin with an additional 10% surviving in a badly crippled state. A higher percentage of cures has been reported following the treatment of miliary tuberculosis with streptomycin. Debré[14] treated 31 children with 15 recoveries; Bunn[15] treated 25 cases with 20 survivors. McDermott[13] estimates that 25% of patients with

FIGURE 4

D. L., 23 mos. old. Primary tuberculosis of lungs, extensive osteitis tuberculosa cystica; cold abscess R shoulder; dactylitis R thumb and L 3rd finger; bilateral tuberculous otitis media; draining sinus R groin following removal of tuberculous epididymis; large mass of tuberculous cervical nodes in L anterior cervical region. Under streptomycin therapy cervical nodes were successfully removed without subsequent sinus formation; drainage from ears stopped but recurred 5 mos. later; sinus in groin closed permanently; cystic disease of bones much improved.

miliary tuberculosis will make satisfactory recoveries following streptomycin therapy. The best results of therapy have been reported when streptomycin was used in combination with a sulfone. Cocchi and Pasquinucci[16] reported 107 cases of tuberculous meningitis; 66 or 62% were alive. With more intensive intrathecal therapy in 52 additional cases, Cocchi[17] claimed even better results; 44 patients survived.

Cocchi's reports and our experience suggest that the combination of a sulfone with streptomycin is advantageous in the treatment of miliary tuberculosis and tuberculous meningitis. We believe that at the present time promizole® is the most valuable sulfone to supplement streptomycin. It has been shown to cause complete arrest of miliary tuberculosis in children when used as the only chemotherapeutic agent. Oral administration and relatively low toxicity allow its continuous use for long periods of time. Recent studies of Pope and Smith[18] may help to explain the mode of action of promizole®. These investigators studied the inhibition of the bacteriostatic effect of sulfones by para-aminobenzoic acid (PABA). They report that the concentration of PABA required for reversal of the activity of promizole® is much higher than that required for any other commonly used sulfones.

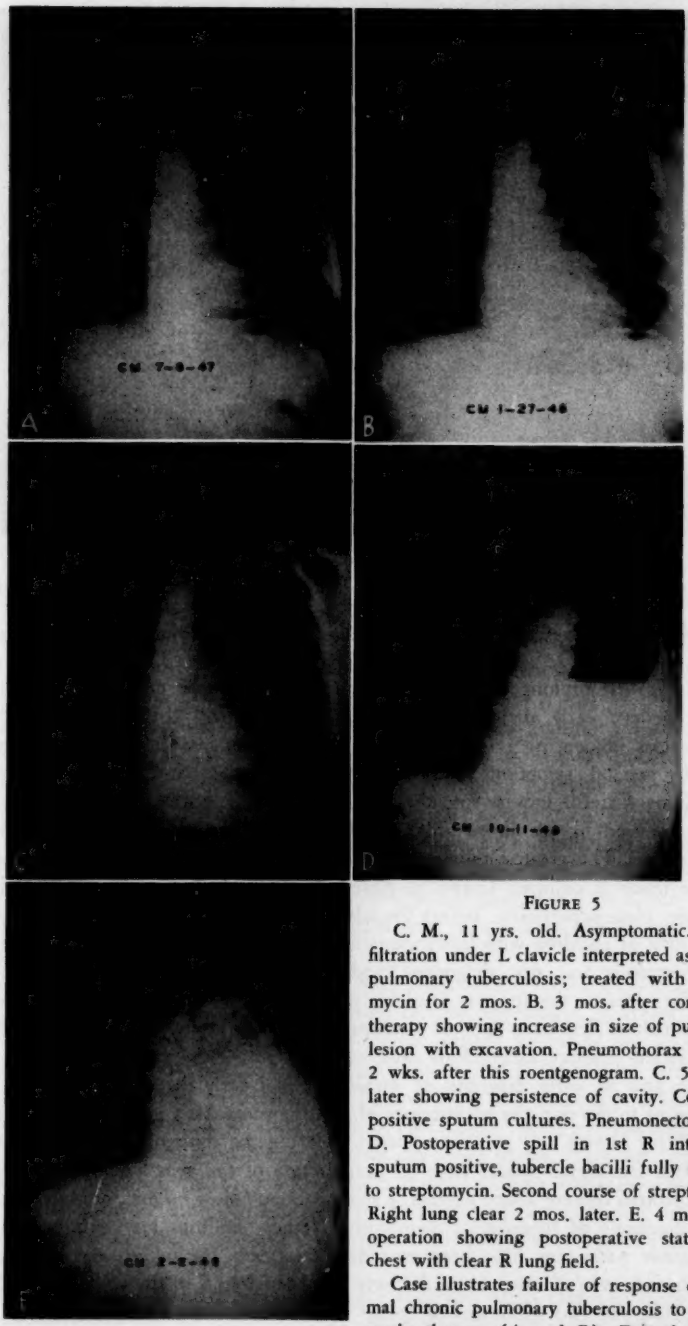

FIGURE 5

C. M., 11 yrs. old. Asymptomatic. A. Infiltration under L clavicle interpreted as chronic pulmonary tuberculosis; treated with streptomycin for 2 mos. B. 3 mos. after completing therapy showing increase in size of pulmonary lesion with excavation. Pneumothorax initiated 2 wks. after this roentgenogram. C. 5½ mos. later showing persistence of cavity. Continued positive sputum cultures. Pneumonectomy left. D. Postoperative spill in 1st R interspace; sputum positive, tubercle bacilli fully sensitive to streptomycin. Second course of streptomycin. Right lung clear 2 mos. later. E. 4 mos. after operation showing postoperative state of L chest with clear R lung field.

Case illustrates failure of response of minimal chronic pulmonary tuberculosis to streptomycin therapy (A and B). D and E show response of recent bronchogenic spread despite previous prolonged streptomycin therapy.

to 37% six months after treatment had been started. More prolonged follow-up, however, has reduced the percentage of survivors.[12] Recently McDermott[13] stated that sustained and satisfactory recoveries may be obtained in 10 to 15% of meningitis cases treated with streptomycin with an additional 10% surviving in a badly crippled state. A higher percentage of cures has been reported following the treatment of miliary tuberculosis with streptomycin. Debré[14] treated 31 children with 15 recoveries; Bunn[15] treated 25 cases with 20 survivors. McDermott[13] estimates that 25% of patients with

FIGURE 4

D. L., 23 mos. old. Primary tuberculosis of lungs, extensive osteitis tuberculosa cystica; cold abscess R shoulder; dactylitis R thumb and L 3rd finger; bilateral tuberculous otitis media; draining sinus R groin following removal of tuberculous epididymis; large mass of tuberculous cervical nodes in L anterior cervical region. Under streptomycin therapy cervical nodes were successfully removed without subsequent sinus formation; drainage from ears stopped but recurred 5 mos. later; sinus in groin closed permanently; cystic disease of bones much improved.

miliary tuberculosis will make satisfactory recoveries following streptomycin therapy. The best results of therapy have been reported when streptomycin was used in combination with a sulfone. Cocchi and Pasquinucci[16] reported 107 cases of tuberculous meningitis; 66 or 62% were alive. With more intensive intrathecal therapy in 52 additional cases, Cocchi[17] claimed even better results; 44 patients survived.

Cocchi's reports and our experience suggest that the combination of a sulfone with streptomycin is advantageous in the treatment of miliary tuberculosis and tuberculous meningitis. We believe that at the present time promizole® is the most valuable sulfone to supplement streptomycin. It has been shown to cause complete arrest of miliary tuberculosis in children when used as the only chemotherapeutic agent. Oral administration and relatively low toxicity allow its continuous use for long periods of time. Recent studies of Pope and Smith[18] may help to explain the mode of action of promizole®. These investigators studied the inhibition of the bacteriostatic effect of sulfones by para-aminobenzoic acid (PABA). They report that the concentration of PABA required for reversal of the activity of promizole® is much higher than that required for any other commonly used sulfones.

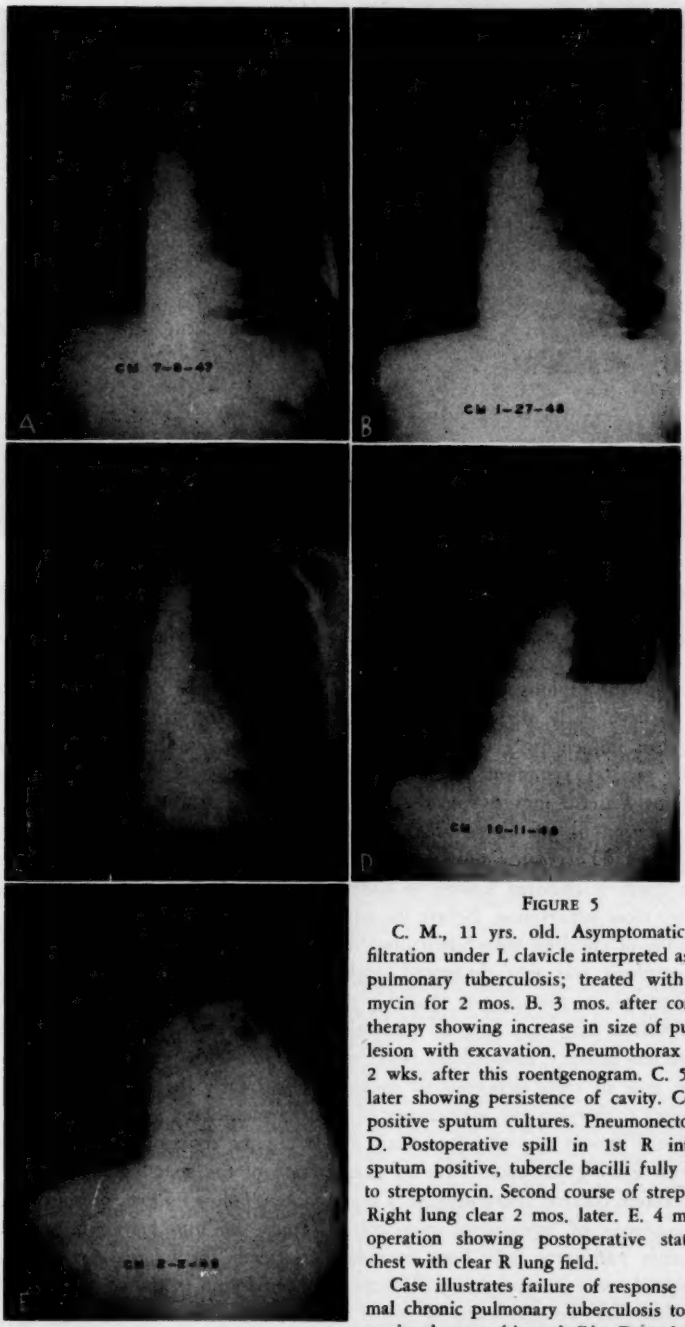

FIGURE 5

C. M., 11 yrs. old. Asymptomatic. A. Infiltration under L clavicle interpreted as chronic pulmonary tuberculosis; treated with streptomycin for 2 mos. B. 3 mos. after completing therapy showing increase in size of pulmonary lesion with excavation. Pneumothorax initiated 2 wks. after this roentgenogram. C. 5½ mos. later showing persistence of cavity. Continued positive sputum cultures. Pneumonectomy left. D. Postoperative spill in 1st R interspace; sputum positive, tubercle bacilli fully sensitive to streptomycin. Second course of streptomycin. Right lung clear 2 mos. later. E. 4 mos. after operation showing postoperative state of L chest with clear R lung field.

Case illustrates failure of response of minimal chronic pulmonary tuberculosis to streptomycin therapy (A and B). D and E show response of recent bronchogenic spread despite previous prolonged streptomycin therapy.

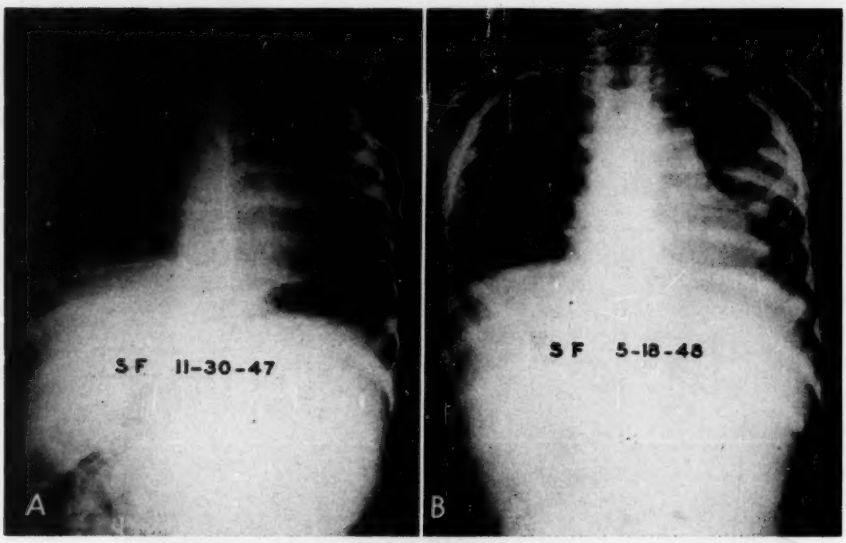

FIGURE 6

S. F., 2 yrs. old. Pneumonic onset of primary tuberculosis treated with streptomycin 1 gm. daily for 60 days. A. Infiltration in 3rd and 4th L interspace and widening of mediastinum on L side consistent with primary pulmonary tuberculosis. B. 6 mos. after onset showing essentially no change.

In addition to the prolonged use of bacteriostatic agents made possible by combined therapy we believe early diagnosis and intensive intrathecal therapy are the most important factors influencing eventual survival. In the great majority of cases of meningitis, early general symptoms such as fever, drowsiness and vomiting precede neurologic signs. Careful inquiry into the family history, tuberculin test and roentgenographic examination of the lungs are helpful aids to diagnosis in any patient with unexplained fever. The greatest number of really early diagnoses of tuberculous meningitis will be made if children known to have recently contracted primary tuberculosis are kept under close supervision. Before the advent of chemotherapy it was found[19] that more than 40% of children with tuberculous meningitis died within three months after primary tuberculosis was first diagnosed, and that more than 60% died within six months. Before specific therapy was available the care and supervision of children with primary tuberculosis may have been of academic interest only; at the present time every child with recent primary tuberculosis must remain under close supervision if we are to attain the goal of early diagnosis of meningitis and early therapy. If we wait for neurologic signs to develop the opportunity of treating meningitis in an early stage may be missed. Every known case of tuberculosis presenting the common general symptoms associated with meningitis should have an examination of the spinal fluid. An increase in cells and protein content above normal, a sugar content below normal, or both, suggest a tentative diagnosis of tuberculous meningitis. If these findings are confirmed in 24 hours and other pathogens have been excluded, treatment for tuberculous meningitis should be started, even if tubercle bacilli have not been found in the spinal fluid. This plan allows time for two specimens of spinal fluid to be collected for culture for later confirmation of the diagnosis. In children with miliary tuberculosis where intramuscular

streptomycin is already being given the chemical values in the spinal fluid, especially the sugar content, may not show a definite change and it is of special importance to watch cases for early general symptoms of meningitis and to treat at once if even only the protein content of the spinal fluid shows a change. As pointed out in the British Medical Research Council report and confirmed by us, the streptomycin level of the spinal fluid may be a valuable guide to the diagnosis of meningitis. With increased permeability of the meninges the level of streptomycin in the spinal fluid tends to increase.

The fact that patients treated during the first stage often develop the full neurologic pattern of meningitis may be due in large part to the irritant effect of intrathecal therapy. Where only intramuscular streptomycin is used as in miliary tuberculosis, good response to therapy is seen much earlier than in meningitis. However, despite the fact that clinical remissions of meningitis have been reported with intramuscular therapy alone, the percentage of remissions is not high enough to justify its exclusive use. Early intrathecal therapy should probably be intensive to the point of toxicity in order to concentrate the drug where the need is greatest.

The three relapses reported here occurred 25, 43 and 45 days after completing streptomycin therapy. The proper duration of therapy is not yet known. It may well be found to vary with the individual case. The spinal fluid should be examined one week after the completion of streptomycin therapy. If the fluid remains normal, the interval between taps is gradually lengthened. Treatment should be resumed immediately if definite chemical changes occur.

The prolongation of life in patients with forms of disease previously fatal has opened special fields of investigation and created a challenging new problem to the clinician. A well-planned cooperative program of all hospital departments including rehabilitation is necessary to fully evaluate each patient and restore him to normal if possible. Caloric stimulation tests, audiograms and electroencephalograms become a necessary routine during the course of treatment in order to determine as early as possible the extent of impairment and the need for correction. Good nursing care and bed rest during the acute stages of illness are essential to the proper care of the child with active forms of tuberculosis. Mental and physical strain must be kept at a minimum and provision made early in the convalescent period for occupational therapy. Toys and picture books and later games that can be enjoyed in bed, story hours, movies and music are all helpful to the patient as well as to the psychiatrist and mental hygienist in evaluating each case.

The selection of patients for treatment with streptomycin requires individual study of each case. Forms of tuberculosis with a high fatality rate should, of course, be treated. When satisfactory progress may be anticipated without chemotherapy as in minimal chronic pulmonary tuberculosis or in primary tuberculosis, the use of streptomycin is contraindicated. Likewise there is no justification for using streptomycin as a means of preventing complications. The development of tuberculous meningitis has been repeatedly reported during streptomycin therapy for miliary tuberculosis. Moreover, isolated complications of hematogenous origin such as in bones or nodes not infrequently develop during or following streptomycin therapy. It should always be borne in mind that unnecessary use of streptomycin may interfere with its later effectiveness in the event of a serious complication.

The whole question of tuberculosis in children still needs intensive study. The most effective regimens will be determined by continued analysis of results obtained in various forms of tuberculosis. Streptomycin is so far the outstanding drug. It is believed

there is some evidence that it may be of even greater value if used in combination with promizole®.

Conclusions

Streptomycin is the most effective tuberculostatic agent. It is unsuitable for prolonged therapy because of its potential toxicity, especially for the vestibular branch of the VIII C nerve, and because of the tendency of the tubercle bacillus to become resistant after relatively short periods of treatment.

Experience only will prove ultimately which lesions respond best to streptomycin therapy. Because of its limitations its use as a sole chemotherapeutic agent should be restricted to cases which can be benefited or cured by short courses of therapy not exceeding six weeks. It is of great value in controlling tuberculosis for short periods of time so as to permit surgical procedures and collapse therapy. Streptomycin is contraindicated in forms of tuberculosis such as primary infections and minimal chronic pulmonary tuberculosis which usually respond without chemotherapy. It should not be used in an attempt to prevent complications; meningitis and other less serious complications may develop during treatment.

Promizole® was found to be ineffective in the treatment of tuberculous meningitis; five out of seven cases of acute generalized miliary tuberculosis treated with promizole® have survived 2½ to almost five years and are free from miliary tuberculosis.

Combined therapy with streptomycin and promizole® was undertaken in order to utilize the advantages of the rapid action of streptomycin with the prolonged bacteriostatic action of the sulfone which can be given safely and effectively for a period of years. By combining the two drugs it was hoped to delay the emergence of resistant organisms and to secure an enhanced effect from both streptomycin and promizole®.

Ten children with miliary tuberculosis have been treated by combined therapy. One patient died after six days of treatment and another of a relapse from meningitis 11 months after the initial diagnosis of miliary tuberculosis. No relapse of miliary tuberculosis has occurred in patients treated with promizole® whether or not it was combined with streptomycin.

Eighteen cases of tuberculous meningitis have been treated with streptomycin by the intramuscular and intrathecal routes and with promizole® orally. Thirteen cases survived from 5 to 23 months. There have been no severe neurologic sequelae. All the survivors are apparently normal mentally.

References

1. Feldman, W. H., Hinshaw, H. C., and Mann, F. S., Effect on previously established tuberculosis of guinea pigs of 4,2′-diaminophenyl-5′-thiazolyl sulfone (promizole), Am. Rev. Tuberc. **50**:418, 1944.
2. Milgram, L., Levitt, I., and Unna, M., Promizole treatment of miliary tuberculosis, Am. Rev. Tuberc. **55**:144, 1947.
3. Lincoln, E. M., Stone, S., and Hoffman, O., Treatment of miliary tuberculosis with promizole, Bull. Johns Hopkins Hosp. **82**:56, 1948.
4. Lincoln, E. M., and Kirmse, T. W., Chemotherapy of miliary tuberculosis and tuberculous meningitis in children, Lancet **1**:767, 1949.
5. Feldman, W. H., Hinshaw, H. C., and Moses, H. E., Promin in experimental tuberculosis, Am. Rev. Tuberc. **45**:303, 1942.
6. Medlar, E. M., and Sasano, K. T., Promin in experimental tuberculosis in guinea pig, Am. Rev. Tuberc. **47**:618, 1943.
7. Smith, M. I., McClosky, W. T., and Emmart, E. W., Influence of streptomycin and promin on proliferation of tubercle bacilli in tissue of albino rat, Proc. Soc. Exper. Biol. & Med. **62**:157, 1946.

8. Kidd, J. G., Modification of tuberculous lesions in patients treated with streptomycin, Bull. New York Acad. Med. **24**:132, 1948.
9. Debré, R., Thieffry, S., and Brissaud, H. E., Streptomycin and tuberculous meningitis in children: Preliminary note, Brit. M. J. **2**:897, 1947.
10. Streptomycin treatment of tuberculous meningitis, Medical Research Council, Lancet 1:582, 1948.
11. Effects of streptomycin on tuberculosis in man: Preliminary statement, Report of the Council on Pharmacy and Chemistry, J.A.M.A. **135**:634, 1947.
12. Streptomycin in treatment of tuberculosis, Report to the Council on Pharmacy and Chemistry, J.A.M.A. **138**:584, 1948.
13. McDermott, W., Bull. New York Acad. Med., to be published.
14. Debré, R., Thieffry, S., and Brissaud, H. E., Méningite tuberculeuse et tuberculose miliaire aiguë chez l'enfant traitée par la streptomycine, Presse méd. **56**:121, 1947.
15. Bunn, P. A., Streptomycin in treatment of human tuberculosis, Dis. of Chest. **14**:670, 1948.
16. Cocchi, C., and Pasquinucci, G., Primi resultati nella terapia delle meningiti tubercolari con la streptomicina associata a solfone e vitamina A, Riv. clin. pediat. **45**:193, 1947.
17. Cocchi, C., Terapia della tubercolosi con streptomicina solfone e vitamin A (Tubercolosi miliare e meningite tubercolare), Riv. clin. pediat. **46**:209, 1948.
18. Pope, H., and Smith, D. T., Am. Rev. Tuberc., to be published.
19. Lincoln, E. M., Tuberculous meningitis in children, Am. Rev. Tuberc. **56**:75, 1947.

SPANISH ABSTRACT

Quimioterapia de Tuberculosis en Niños

La estreptomicina es el agente tuberculostático más eficaz, pero es inadecuado para terapia prolongada a causa de su toxicidad potencial y la tendencia del vacilo tuberculo a volverse resistente a ella.

La estreptomicina es de gran valor en controlar la tuberculosis de manera que permita procedimientos quirúrgicos y terapia de postración. No se debe de usar en tuberculosis primaria que no sea complicada ni en tuberculosis pulmonar crónica porque estas formas de la enfermedad generalmente responden al manejo conservativo. No debe de usarse para tratar de evitar complicaciones; meningitis y complicaciones menos serias pueden desarrollarse durante el tratamiento.

Se trataron siete pacientes con tuberculosis miliar aguda generalizada con una sulfona, promizole®. Cinco de ellos están viviendo de 2-½ a 5 años después que se principió el tratamiento. Las motas miliares pulmonares desaparecieron completamente en un promedio de 8 meses. No hubieron casos de recaída y ninguno de los pacientes desarrolló meningitis.

Se emprendió la terapia combina con estreptomicina y promizole® para utilizar las ventajas de la acción rápida del antibiótico con la acción bacteriostática prolongada de la sulfona. La promizole® puede ser dada con seguridad y eficazmente por años.

En el tratamiento de tuberculosis miliar mediante terapia combinada, 1.0 gm. la estreptomicina (0.5 gm., dos veces al día) se da intramuscularmente por 120 días. 1.0 a 8.0 gm. promizole® (0.25 a 2.0 gm., 4 veces al día) se da oralmente por 3 años. La dosis original de 1.0 gm. diaria se da por varios días. En la ausencia de señas de toxicidad, un aumento gradual de 1.0 a 2.0 gm., o más se hace cada cuantos días o semanalmente hasta que las cantidades de promizole® de sangre terapeutica (tomada 3 horas después de la última dosis oral) entre 1.0 y 3.0 mg./100 cc. son obtenidas. Diez pacientes con tuberculosis miliar fueron tratados mediante terapia combinada. Ocho quedaron bien de 6 a 23 meses después de que se principió el tratamiento. Las motas miliares pulmonares desaparecieron en un promedio de 9 semanas. No hubo recaída de tuberculosis miliar, pero los sobrevivientes que desarrollaron meningitis se han restablecido bastante.

En el tratamiento de meningitis de tuberculosis mediante terapia combinada, la estreptomicina 1.0 gm. se da intramuscularmente por 180 días. En adición, se da 0.1 gm. intratecalmente una vez al día hasta que vengan los síntomas tóxicos. Después de eso, esta cantidad se da cada dos días; pero si los síntomas ocurren de nuevo, se dan 0.05 gm. cada 2 o 3 días hasta que una serie de 40 inyecciones ha sido completada. La promizole® se administra por el mismo método prescrito para la tuberculosis miliar. Se han tratado 18 casos de meningitis de tuberculosis por este método. Trece pacientes sobrevivieron de 5 a 23 meses después de principiar la terapia. Todos los sobrevivientes parecen estar normales mentalmente.

492 First Avenue

Pediatrics

VOLUME 5 FEBRUARY 1950 NUMBER 2

AMERICAN ACADEMY OF PEDIATRICS, INC. PROCEEDINGS AND REPORTS

Round Table Discussion

PARENT-CHILD RELATIONSHIP IN THE EMOTIONAL DEVELOPMENT OF THE CHILD

HALE F. SHIRLEY, M.D., San Francisco, Calif., and MARY H. LAYMAN, M.D., San Francisco, Calif., *Chairmen;* JAMES F. CLANCY, M.D., Hammond, Ind., and MARGARET A. LIMPER, M.D., Louisville, Ky., *Secretaries*

I. TWO BASIC CONCEPTS IN EMOTIONAL DEVELOPMENT

Chairman Shirley: There is a story which everyone responsible for the care and training of children should know: A lady living in a swanky hotel complained to the manager that the occupant of the suite next to hers kept pounding the piano at all hours. Not only did he make frequent discords, but he monotonously played certain passages over and over far into the night. She said that this was getting on her nerves. She did not believe she could stand it much longer. In fact, she was afraid if something was not done about it, she would have a nervous breakdown or do something desperate.

The manager said, "Well, lady, don't you know who is playing the piano?"

"No," she said, "Who?"

"Why," he replied, "it is the great ————! He's practicing for a concert tour."

"Is that so?" she exclaimed, "Well, I declare!"

So she went back to her room and listened with increasing interest. She invited her friends to listen. They had their meals brought up to the room and listened far into the night; they did not want to miss a single note!

It was the same music, but a different point of view.

So when parents, anxious, frustrated, resentful and worn out, come to the pediatrician and complain that their children just will not play the music of life sweetly, that although they hold up the most beautiful scores before their offspring, the most gosh-awful noises come out, it would seem to be time for physician and mother to sit down and think through together just who is making these discords in the emotional atmosphere of the home. What is the nature of this perpetrator of deafening racket? What is the meaning of the intolerable noises he creates? What is he attempting to accomplish? For it is only from the standpoint of understanding that we as physicians and parents can get the greatest enjoyment from our children, guide them most effectively and tolerate their childish behavior with some degree of equanimity.

From the Annual Meeting of the American Academy of Pediatrics, San Francisco, Calif., Nov. 14-15, 1949.

Common Parental Viewpoints

In pediatric practice, one constantly encounters several parental viewpoints in regard to the child. We might mention first that of the mother with her first, much wanted child. To such a mother, her baby is a little angel. He is perfect. In him there can be no guile. For several months after his arrival, his mama and papa say to themselves, "Now, if we can only be perfect parents, we will have a perfect child. If we can avoid making mistakes in his training, he will do just what we want him to and will become just what we want him to be. There will be no friction in *our* home. The life of *our* child is going to be just one long symphony of melody and harmony."

This is, indeed, a beautiful theory, delightful to dwell upon, and it lasts about one year. Sometime during the second year mama says to papa, "Daddy, I just don't know what is getting into our little Johnnie; he has been so naughty of late. When I tell him to do something, he says, 'No' and 'I won't!' When I tell him not to do something, he goes right ahead and does it. He keeps getting into everything, and if I spank him, he just gets mean and stubborn."

This startles papa, and after a few minutes of painful thought, he expresses the opinion that it must be the Old Nick in the child that is coming out. "By the way," he says to his wife, "you had a brother who got into some trouble, didn't you?" To which the wife retorts, "Yeah, and your father was no angel, was he?"

But our young parents are brave. They are determined to face and fight the evil tendencies apparently inherent in human nature. They will proceed on the theory that the child is a little devil if they have to. Just let a wicked thought or deed appear in *their* child and they will nip it in the bud! Thus they become primarily concerned with what in the child's behavior is good and bad. Bad behavior cannot be tolerated. Their child is going to be good, or else!

But this "little devil" theory is not a beautiful one, and it is highly frustrating. The parents, finding that there seems to be no end to the child's resources of rascality, begin to wonder if there is not some other explanation for Johnnie's unacceptable behavior. They talk to the neighbors. They read magazines and books. Sooner or later, they come up with a theory which sounds promising. According to this theory, the child is like a puppet; if the parents pull the right strings, he will jump the way they want him to. One trouble with this theory is that it is hard to find out just what strings to pull. And even when the parents do locate someone who is willing to play the role of an authority, they pull the string recommended and, lo and behold, the child jumps in the contrary direction.

Parents now are likely to go into another huddle with the authorities and come up with a modification of the puppet theory which we may call the "putty theory." According to this theory, the child can be molded into any shape provided you apply pressure in the right places. So the parents start putting on pressure. Maybe this works. Often it does not. The parents may find that pressure applied in one place produces unexpected and undesirable bulges in another. Too often, too, the parents find that the method backfires and that they are the ones who experience the pressure. The only people who are unaware of the pressures which children can exert upon their parents are people who do not have children.

By now, our parents are thoroughly frustrated and alarmed. They begin to wonder if there can be something seriously wrong with their Johnnie, some part of him which is not working right. Maybe it is his tonsils, or his spinal column, or his flat feet causing the trouble. Maybe he needs some vitamins or endocrines. On the theory now that their child is a little machine thrown out of whack by some faultily functioning part, they seek the aid of their physician. Maybe the physician does find something organically wrong which needs correction. Often, though, he does not, leaving with the parents the haunting fear that there may be something wrong with the child's mind.

If the parents do not get help at this stage of their difficulties, they are most likely to fall back upon the time-honored, socially acceptable and morally unassailable theory that the child is a little adult. This theory can be called the "dwarf theory." If one wants to be facetious, one can call it the "homunculus theory." According to this theory, the child should behave like a little adult. When he does not, measures as drastic as necessary should be taken to correct his behavior. Even parents who, on questioning, would readily admit that their child is but a child, often, more or less unaware of what they are doing, proceed on this theory.

Why they do so is readily understandable. When the parents themselves were children, they were corrected, blamed and punished for childish behavior. They experienced frustration, anger, hostility, anxiety and guilt in connection with their own behavior and in relationship to their own

parents. As they more or less successfully solved these behavior and emotional problems, they acquired strong feelings of what is right and wrong, proper and improper. As adults, they strive to act in accordance with their consciences. But when they see their child doing something which they feel is bad, such as sucking his thumb, their old childish feelings are reactivated. They become filled with anxiety, disgust and anger. Such feelings, and not the logic of the situation, drive them to attempt to put a stop to the child's behavior.

This chain of events, of course, is only natural. It is the main method by which culture has been transmitted from one generation to another. It is one way through which children become socialized. But it is also the process through which parental immaturities, prejudices and emotional dilemmas become established in the personalities of children. Rigorous application of the "little adult" theory results in constant conflict, frustration and emotional upheavals in the home which are anything but conducive to the normal emotional development of the child. The theory may eventually turn out to be right. In 20 years or more, the child in spite of obstacles may turn out to be a little adult. But he also may not. The world is still full of people who are physically mature and sometimes even intellectually superior, who vote or in other ways determine the course of civilization, but who still think and feel in childish ways.

But if, on the one hand, an inadequate concept of the nature of the child proves sometimes to be a handicap to parents, the tremendous increase in psychologic knowledge during the past generation, on the other, has not been an unmixed blessing to parents. It has put them on the spot; made them self-conscious, anxious and defensive. Conflicting views of authorities have bewildered them. Parents have been led to believe that the slightest deviations from the average and certain behavior patterns which are often nothing more than normal child behavior may, if not nipped in the bud, develop into momentous and tragic trends in later life. They have been given to understand that there are no behavior-problem-children, only behavior-problem-parents.

As a result, parents have begun to feel that it is wrong for them to be human beings. They have become afraid to be natural with their children—afraid to love them, afraid to feel angry with them, afraid to be lenient with them and afraid to be firm. In addition to bewilderment and anxiety, they have experienced great frustration and feelings of guilt. Trying desperately as they do to be good parents, they can never feel the satisfaction from the belief that they are succeeding.

Now, the purpose of this discussion is not to poke fun at parental short-comings, nor is it to proclaim that children at times are not little demons. Each of the parental viewpoints described has something of value. The point is that no one of them, nor even all of them put together, give an adequate picture of the child, adequate for either parents, teachers or doctors who wish to help sincere parents deal wisely with their children.

Emotionally disturbed parents, of course, need help with their own feelings. They need understanding, sympathy, encouragement, renewed faith in their children and increased confidence in themselves. Counselling parents to be perfect is a waste of breath. Telling parents to be calm, unemotional, logical, truthful and consistent is apt only to add to their feelings of inadequacy and guilt. The parents may very well need knowledge, but knowledge can be of use only as it is brought into harmony with their own personality trends and emotional adjustment. The pediatrician, therefore, is frequently confronted with situations in which children can be helped only if the parents can seek and make use of help for their own emotional difficulties.

There are, however, two concepts, quite new historically, which the author believes are basic in understanding personality development. He further believes that when these ideas become more generally accepted by parents, they will add to parental understanding of childhood behavior and will increase the satisfaction and security felt in playing parental roles. Certainly, life will be happier for both parents and children if pediatricians constantly emphasize the fact that the child is not a little adult, that he does not think like a little adult, he does not feel like a little adult, and he can not behave like a little adult except for short periods when under strong pressure. For between infancy and adulthood, two processess, both of fundamental importance, are taking place. One is growth and the other is learning.

Emotional Growth

As physicians, we are thoroughly familiar with physical growth. Psychologists, also, have taught us a great deal about mental growth, so we now think of mental development in terms of mental age. We can no longer, however, remain unaware of the significance of emotional growth. Perhaps

we do not know as much about emotional growth as we do about physical and intellectual growth. For one thing, our measurements of emotional reactions are by no means clear cut and objective. For another, emotional maturity can only be relative, like perfection, seldom if ever completely attained. Yet our present understanding of personality development is greatly based upon the concept of emotional development and the factors which foster or prevent the eventual attainment of a high degree of emotional maturity. The emotional development of the child, therefore, is a fertile field of research.

The journey from the emotional make-up of the infant to that of the emotionally mature adult is a long, hard one, fraught with many hazards and pitfalls. The infant starts out life not only absolutely ignorant and inexperienced, but emotionally as well as physically dependent upon his parents. He has no emotional control. He acts promptly on impulse. He wants what he wants when he wants it. His primary interest is in himself. He is largely preoccupied with his own bodily sensations. He has no sense of right and wrong. His one method of satisfying his needs and of controlling his environment is an attention-getting mechanism, his cry, which, incidentally, every pediatrician will agree is usually highly effective.

The first year of the child's life, from the standpoint of emotional development, is largely characterized by differentiation of the undefined emotional tension of the newborn into the toddler's rich repertoire of basic emotional reactions. As the child grows in experience, he learns to differentiate himself from his environment and to evaluate his capacities and limitations. In the second year, during the so-called stage of "resistance" or "negativism," he shows the first signs of his need to become independent and to be regarded as an individual in his own right. In family and social living, he must learn to acquire some degree of emotional control. He must acquire feelings of right and wrong which will keep him out of serious trouble and yet not keep him in constant misery because he cannot attain perfection. He must learn to forego certain immediate pleasures for satisfactions which have greater personal and social value. He must pass through a long developmental process of his capacity to love, experiencing first the satisfactions of self love, then successively developing constructive emotional attachments to his parents, siblings, playmates and eventually to a mate with whom he can found a home and family, and finally arriving at full emotional maturity with good will if not love for his fellowmen, those outside as well as within his particular group.

The concept of emotional maturity has two important clinical applications. First, one cannot hurry emotional growth any more than one can hurry physical or mental growth. It is probable that every child has his own individual rate of emotional growth, though the sequence of emotional stages are inherently the same for all children. Incidentally, it is a fact as well as a source of maladjustment of common experience that the rate of emotional growth does not always parallel physical and mental growth.

A point which often must be made clear to parents, therefore, is that a child should be allowed to be his age. He must experience the satisfactions and solve the emotional problems of his age, not those of the adult. It is only thus that he is ready and able to take the next step on his journey to emotional maturity. Emotional readiness, no less than physiologic and intellectual readiness, is necessary before a child can be led to adopt the next more mature type of behavior.

In giving the parents this insight into the nature of their children, it is often necessary to build up their confidence in the inherent potentiality and normal drive within children for emotional development and the attainment in due time of emotional maturity. It may be that there are a few defective children who are not capable of attaining emotional maturity. It may be that there are individual differences in the degree of emotional maturity which people can attain. Certainly there is no question but that deprivations, unwise pressures and poor adult example can distort and stunt emotional growth, just as inadequate diet, lack of shelter and the inroads of disease can interfere with physical development. We know, too, that parents who lack faith in their children are most likely to provoke unnecessary emotional disturbance in their children, yet there is sufficient reason to believe that when we provide in our homes and schools the right kind of emotional atmosphere for our children, we can confidently put great faith in their innate power for growth and social integration.

The second clinical usefulness of the emotional development concept is the help which it gives us in understanding abnormal and antisocial adult behavior. We are beginning to realize that most of the mentally ill, criminal and emotionally handicapped individuals of our society are failing in their social adjustment because they have never grown up emotionally. They have become stuck at some

stage of their emotional development. They are still struggling along with unresolved childhood emotional conflicts. Either experiences which undermined their sense of security and self-respect or frustrations which were beyond their ability to overcome have left such people with deep feelings of insecurity, inadequacy, hostility or guilt, which cripple them in living just as surely as if they had acquired a deformed leg or a leaky heart. Unwholesome interpersonal relationships in childhood have become the intrapersonal emotional conflicts and faulty attitudes of adulthood.

But it isn't only those who are recognized as mentally ill or criminal who are emotionally immature. Our wars, both hot and cold, our inability to solve economic problems, and our failure so far to achieve world government and the brotherhood of man are due in great part to infantile and childish attitudes and feelings which our populations have been unable sufficiently to outgrow. World affairs are still dominated by immaturities such as selfishness, neurotic anxieties, exaggerated competitiveness, irrational hostilities and group prejudices. The most important problems which we as a nation and world face today, therefore, have to do with how we can help people to grow up emotionally. Probably the main task of parents, aside from satisfying children's physical needs, is for them to create a home atmosphere which is most conducive to the child's attainment of emotional maturity. And one of our main jobs as physicians is to help parents do just this.

But before we continue with a discussion of the environmental factors which encourage or thwart emotional development, it is necessary to bring in one more concept which is fundamental in understanding personality development.

Personality Development as the Result of Forces

It is helpful to think of childhood behavior and personality development as the resultant of two groups of forces, though both are infinitely complex. There are the forces which come from within the individual due to the fact that each person has inherited the characteristics and potentialities of the human being, and there are the forces exerted upon the individual from without, due to the fact that the human being must live in a physical and cultural environment.

In studying human behavior, one cannot separate the individual from his environment. There is no such thing as a child brought up in a social vacuum. One cannot even adequately think of the infant except as a part of a child-mother if not a child-mother-father unit, living in a certain cultural environment. The infant, it has been well said, can be defined as an island of human potentiality surrounded by mother. As he grows, his immediate environment expands to include his father, his siblings and other children, and his teacher. It is not long before his world begins to include his whole community. In recent years, we in this country have painfully learned that the adult world is about 25,000 miles in circumference and contains about 2,000,000,000 people. It is far from being an ideal world. In this world, the adult must find his little niche. He must find a position of social usefulness if he is to support himself and his family. He must also find friendship and love, some satisfaction and happiness in life, and, incidentally, fight like heck to keep from being run over.

The Inner Forces

From the dynamic standpoint, we can best think of the "inner forces" in terms of needs and drives. As physicians, of course, we are thoroughly familiar with the physical needs of the child. We are also more or less clearly aware of the many drives which, inherent or not, we see developing in our children in response to environmental and cultural stimulation: drives for action, exploration, acquisition, power, personality integrity, orientation and integration—drives which the author likes to think of simply as tendencies to become a normal human being. Of no less significance in the understanding of human behavior, however, are the emotional needs, which though sometimes less obvious are of fundamental importance in living: the needs for love, security, self-respect, self-confidence, and support as well as guidance throughout the period of growth and learning.

In early infancy, the child's need is the mother's command. When the child's behavior, in his cry, in effect says to the mother, "I need," mother says, "You shall have," and father says, "You bet your life, he shall have." Society says, "If your father and mother do not give it to you, we will pass a law seeing that you get it." From the dynamic standpoint, then, the forces in this situation are all in harmony. Everything is working out for the welfare of the baby, the happiness of the parents and the glorification of mankind.

The Outer Forces

But this ideal situation does not last long. The time comes when our little Johnnie begins to want something which is not in line with the "outside forces." Johnnie lives in a social and cultural world which for many generations has been accumulating convictions as to what little boys and girls should and should not do. Johnnie's parents also live in this world and society expects them not only to keep Johnnie in line with the social rules, but to bring him up as nearly as they can in the footsteps of the saints, the heroes and the great of the past. So sometimes when Johnnie says, "I want" or "I will" or "I won't," mother says, "You can't have" or "You must not" or "You must." If Johnnie shows a goodly amount of what it takes to get along in this world and persists along the line of "I will," mother says in effect, "If you do, you won't be loved. You will find yourself in disgrace. You will be in the doghouse." If that does not seem likely to thwart Johnnie, she adds, "If you do, you will be punished!"

The child and his parents thus find themselves locked in conflict. This is where we as physicians are called upon to step in. This is where important things are taking place—important from the emotional and behavioral standpoints, and important both for the happiness of the family and the future welfare of the child.

Emotional Reactions at the Point of Conflict

Let us consider for a moment what does take place at this point of conflict from the emotional standpoint. We need not discuss what the neighbors think because we are all aware of that. Those of us who are parents also are thoroughly familiar with the perplexity, anxiety, anger and guilt which we ourselves feel when we are faced with the intransigency of our offspring. A little introspection also will give us some clue as to how the child feels. How do we feel if we are thwarted? Angry, don't we? How do we feel if the weight and majesty of the law or the condemnation of our fellow man threatens to cave in on us like a ton of bricks? Anxious, don't we? And so does the child. In the frustrated child, then, we have to deal with a hostile or an anxiety reaction, or both.

Normal Emotional Functioning

Anger and fear reactions are perfectly normal human responses. They have a normal role to play in human living. Anger prepares the organism physiologically to overcome resistances. Fear is protective; it prepares the organism to fight or run. Anxiety warns the person that he may be in danger. It is an unpleasant state of feeling, so it drives the person to do something to get relief from it. It may drive the individual to adopt either aggressive or defensive tactics.

Anger reactions are common in children. Most small children thoroughly try out the temper tantrum, and they tend to make frequent use of it if it works out to their advantage. And in later childhood or even adolescence, there is no cause for alarm if hostilities and resentments occasionally accumulate to the point of explosion. It is probably impossible for a child to learn to adjust to our culture without thwartings and frustrations which result in some emotional distress. Sometimes it is wise to let the child get rid of his strong feelings in an emotional outburst. Certainly there is no good reason for parents to be hurt too much if a child in a fit of anger describes them unfavorably or suggests where it is fitting that they go.

But when hostile or anxiety reactions are frequent, severe or chronic, and when they thus dominate the life of the child, the situation is hazardous for the child's welfare. Uncontrolled anger after infancy is a serious social handicap, and chronic anxiety is apt to be more crippling than regulative. So when these emotional disturbances remain beyond the child's control and produce symptoms of serious maladjustment, we must go back in our thinking to the point of conflict and decide what we can do to reduce the conflict, change the child's feelings and thus reverse the trend.

Technics of Adjustment

Fortunately the conflict is not always as inevitable as what has been said might lead one to believe. The collision of forces is not always like the one which occurs when an irresistible body hits an immovable one. Sometimes the nature and extent of parental demands can be modified with benefit. In addition to that, however, changes are taking place within the child which, with the understanding and help of the parents, may make it possible for him to satisfy his needs and wants in ways which are socially acceptable. The child, as he grows older, is constantly gaining in ability to think and

reason. He is growing in experience. And when he finds that his desires are balked, he can experiment with possible ways of solving the dilemma.

Let us suppose, to make use of a simple illustration, that what Johnnie wants is a piece of candy which he has seen in the cupboard. His mother has told him he cannot have it until after supper for dessert. She has said that if he takes it, she will be angry with him. Not only that, she will turn him over her knee and use the hair brush.

In this situation, Johnnie has to weigh several factors: How hungry is he? How good would the candy be? How much does his mother's approval mean to him? What are the chances he could get away with it? How much would a spanking hurt?

Depending upon his decision as to these factors, there are many possibilities for action. He can say to himself, "I'm not very hungry and the candy wouldn't be very good anyway, so I'll just forget about it and go out to play." Or he can say to himself, "Oh, how hungry I am! I can hardly stand it. How I wish I could eat that candy!" So he daydreams about it, and the following night he dreams that he is in a fairyland in which everything is made of candy. Or, he can recall that his mother said he can have an apple whenever he wants one. So he eats an apple, which satisfies his hunger, and thinks no more of the candy. Or, he can refrain from eating the candy but remain angry about it, thinking, "How mean my mother is for not letting me eat that candy! I'll get even with her. I just won't eat any supper tonight. Will that make her worried!"

But maybe, on the other hand, Johnnie eats the candy. Perhaps mother forgets all about it and he gets by with it. Possibly, though, he feels so guilty about it that he pesters his mother until she punishes him so he can start off with a clean slate. Maybe he takes the punishment in his stride; it wasn't bad and the candy was delicious. Or perhaps he denies that he took the candy. He may put the blame on his little sister who is too young to know if she took it or not. He may even work on his mother's sympathy by telling her that he didn't want to take it, but he was just so hungry he couldn't help it. Or he may say, "Mother, I ate it, but it wasn't my fault. A big boy came here and held me down and poked it right down my throat!"

These ways of dealing with human impulses and environmental pressures are known as adjustive technics. Psychiatrists have big words for them. It is obvious that some of them are more effective than others. Some clearly, also, are immature and some mature. Some are satisfying to the individual but socially unacceptable. Some get the individual by socially but are dissatisfying personally. The child, by trial and error and through imitation of people around him, tries out various methods of solving his problems. He continues and establishes by habit those which work best. If he thus comes into adulthood equipped only with immature, grossly unsatisfying, or antisocial technics of adjustment, he is a severely handicapped individual.

It is, therefore, a primary function of parents and teachers to help children by instruction and example to learn methods of satisfying their normal, fundamental needs in ways which are socially acceptable. That does not mean that every whim and fancy of the child should be gratified, or that restraint and repression are not often necessary for social adjustment. But there are certain basic human needs which must be fulfilled to some extent before social adjustment is possible for the child.

Emotional Imbalance

But suppose that the child cannot find a satisfying or acceptable line of action. Suppose that his need is so great, his environment is so restrictive, or his parents are so blind or ineffective that they do not furnish sufficient guidance for him to learn effective methods of adjustment—what happens then? The answer is that the child is thrown out of emotional balance. His hostilities or anxieties accumulate to the point that he cannot deal with them. They begin to cause symptoms. Although the feeling state of the maladjusted individual is always complex in that both anxiety and hostility as well as other feelings are usually present in some degree, one feeling or another may predominate, and we have to deal primarily with a hostile child, or an anxious child, or possibly a defeatist child.

The Hostile Child

Excessive and chronic hostility becomes manifest in the child's behavior in many ways. There are likely to be frequent, severe and often prolonged anger outbursts. The child is likely to display a negativistic, punitive attitude toward his parents, refusing to eat, persisting in soiling and wetting, objecting to going to bed, ignoring parental requests, being deliberately disobedient, and becoming

evasive if not disrespectful and rebellious in attitude. Such a child is also likely to be pugnacious with other children, going around with a chip on his shoulder and fighting at the drop of the hat at fancied as well as real insults. There is apt to be marked jealousy of siblings. The hostile child also eventually becomes prone to pick friends from among children with antisocial attitudes, more and more identifying himself with delinquent groups if the trend is not reversed.

The Anxious Child

The child suffering from intense and prolonged anxiety tends to become timid, shy, inclined to daydream, often afraid to try, and likely not to make the best use of his capacities. He may on the other hand overcompensate for his anxiety by becoming overly aggressive and hostile. Many anxious children are tense, irritable, restless, hyperactive and explosive. Nervous habits abound among them: finger sucking, nail biting, bed wetting, tics, night terrors and the like. The chronic emotional tension, also, is likely to interfere with physiologic functions, making the child overconscious of his bodily sensations or resulting in such symptoms as abdominal distress, vomiting, headache, diarrhea, and various aches and pains. Occasionally, anxiety attacks, hysterical features or obsessive-compulsive symptoms develop.

The Defeatist Child

The child may, however, give in to frustration. Although he may feel some anger and anxiety, he may refuse, actively, to fight for a satisfactory solution. His parents complain that he just will not try. He insists that he cannot do things. Constant failure feeds his feelings of inadequacy and inferiority until he grossly fails to develop his capacities and gradually withdraws from social contacts into fantasy or utter defeat.

Conclusion

These, then, are two basic concepts which parents can well add to their viewpoint of the child and of childhood behavior: (1) that of emotional growth and (2) that of the emotional disturbances which children undergo when they cannot learn to satisfy their normal human needs in a reasonably socially acceptable way. It is worth emphasizing that you cannot understand a child's behavior until you know how he feels, and you cannot change his behavior until you know what can be done to change his feelings. Usually you cannot change his feelings until you understand what his needs are, and which needs, by his behavior, he is attempting to fulfill.

II. ENVIRONMENTAL FACTORS IN EMOTIONAL DEVELOPMENT

Chairman Layman: In the preceding paper we have followed the emotional development of the child, his needs, his drives and the basic causes for their happy unfolding as well as for their tragic frustrations.

Now, to further complicate matters, I am going to introduce the innumerable environmental factors which constantly mold and modify this basic pattern.

"The first cry of the infant is a cry of wrath at the tragedy of being born." So said Kant, the German philosopher, about 100 years ago. His world at that time was rife with many serious conflicts and upheavals, nor has it improved much since then, in fact, some think it has gone from bad to worse, and that the infant may be justified in dreading to come to grips with it. I doubt whether we can, like Kant, credit the infant with sufficient wisdom to recognize this perplexing situation in the very first hour of his existence; however, we do know, that when he has grown to childhood and adulthood, his "wrath" only too frequently finds expression—expression in ways fatal to himself and others.

We see this manifested in ever increasing aggressive behavior of the individual and groups and nations. Assault and battery are on the increase; disregard and acquisition of other people's property; murder in the back alley and on the international scale; not to speak of the seemingly minor acts of aggressiveness in business, professional and social life.

We see it in the steadily increasing disruption of the home life by the rising number of divorces, the percentage of which ranges from 10% or less in stable, homogeneous sections of the country to 100% in Hollywood, making a national average of 25%, or one divorce in every four marriages. Divorce is such an accepted marital concomitant, that when I recently passed around a newspaper

clipping of a wedding announcement to my associates, they saw nothing startling in the fact that "for both parties this is their first marriage."

And finally, we see man's "wrath" increasingly directed toward himself in complete helplessness and despair, when he escapes into the unrealities of insanity or complete annihilation through suicide, culminating in the prospective race suicide by atomic bomb!

The foregoing paper has shown that human nature offers as many constructive potentials as destructive ones. What then has the world, what has the environment contributed to so often mar or at times even crush man's potentials for happiness and success, while letting his destructive ones run amok?

I do not want to draw too black a picture; I am really not that much of a pessimist. We will agree, that there are many happy, successful individuals in this world, well able to cope with the exigencies of life with a minimum of emotional upset to themselves and the least damaging results to others. But there are too few. Too much good material is wasted. And, above all, the group of maladjusted people makes it pretty tough for those who otherwise could make their peace with the world.

There are also a goodly number of thinkers and knowers who could improve the lot of those people we call failures, and who are actually doing it day by day. But progress is slow as in all evolutionary processes, and time is now of the essence with world destruction staring us in the face.

So, the sooner and more often we can exchange knowledge and experience—limited as this may be as yet—on the whys and wherefores of human behavior and "spread the gospel," the better is our chance of more effectively handling it.

Even small meetings like this are not just a drop in the bucket, nor should anyone let himself be overwhelmed by the magnitude of the task; physicians well know that only a good dose of optimism enables them to meet their challenges. "The challenge of the 20th century is the challenge of human relations," said President Truman at the recent cornerstone laying of the United Nations building.

It is an old story that each succeeding generation while in the process of adjusting to an environment created by its preceding generation finds itself already outdistanced by it; but never has the change been as rapid as it is nowadays, nor have there been such a number of new and intensive influences condensed into such a brief period of time.

The material benefits accruing in the present age cannot be questioned—of mental and spiritual indigestion we are painfully aware. At the same time we are still sadly ignorant of the extent and importance of the numerous and varied environmental influences and desperately trying to analyze them.

Up to the turn of the century, attitudes and reactions as observed on the adult level were projected onto the child as onto a "little adult," whereas modern trends are beginning to demonstrate that the child is not a small replica of the adult at all. He is an individual *"in statu nascendi,"* in the process of growth, with potentials of receptiveness and reactions that are specific for the various growth levels, and which differ widely from those in the adult.

Intellectually, his lack of experience limits the child's vision, his appreciation of consequences; his meager store of information cannot satisfactorily meet his curiosity and, therefore, finds its answer in the realm of fantasy, in which the real and the imaginary blend throughout childhood. Language, the main means of communication between the individual and the world, but also one of the greatest sources of misunderstanding at best, constitutes a definitive hazard for the child. In this very circumscribed world of his, the child under 10 cannot well generalize, compare or evaluate; he must, of necessity, reach his interpretations from the viewpoint of his own personal limited knowledge.

Now, we know that the child feels rather than thinks, and that, whereas his emotional life also follows a developmental pattern just as his physical and his intellectual growth and other trends do, his basic emotional functions—in contrast to the intellectual ones—are already well established at birth. How strongly dominant human emotions remain as compared with the intellect is quite evident in human behavior all through life, from the bawling of the infant in his effort to secure his bottle to the United Nations delegate's vituperations in an attempt to reach his objectives.

Perhaps a glance at a chart on evolution, as the geologist sees it, will illustrate this relationship.

If we assume an interval of 1,000,000,000 years since the appearance of the most minute soft

tissued life, of which, say, the amoeba would be representative, and follow evolution through the great periods called archeozoic, proterozoic and so on to the most recent, the cenozoic, we find at this stage the appearance of the first warm blooded animals in the last 4% of one billion years, and man himself only in, more or less ½% of this 4%, or about 200,000 years.

In the amoeba it would be difficult to recognize anything similar to what we call intelligence, but we certainly do see an incipient primitive emotional reaction in the reaching and withdrawal of its pseudopodia, attraction and rejection, the basis of love and hate, and the possibilities of satisfactions and frustrations.

These figures and deductions are, of course, arbitrary, but they do present a vivid picture of the discrepancies in our intellectual and emotional life, the solid entrenchment of emotion through the ages as against the comparatively recent and therefore still precariously functioning mentality.

On the other hand, this progression also allows us the hope that the next steps in evolution may enable this precarious instrument, our mentality, to develop to a level which will permit a somewhat better balance and efficiency in human behavior.

What then does our present environment do to further or to check this evolutionary development in the child? Since the environment in our civilization is mainly created by man himself, it also lies within his power to modify it, once he learns how to do it.

Dr. Shirley has just neatly outlined for you the nature of the human material with its manifold potentials and typical reaction patterns. It is now my task to review with you the nurture of this material under the impact of the environmental factors.

At this session time and space will not permit of considering all factors involved. In the next half hour or so I shall touch only on the highlights and leave further particulars to later discussion.

Factors in the Community—Direct Influences

Let us divide the environmental factors into two large groups, those in the community and those in the home. The former are the more obvious—the latter are the most important.

It is quite evident that the impact of what children see and hear should be considered of paramount importance in their development, since it is the visual and auditory media which our civilization has perfected to a degree heretofore unknown.

The newspapers, magazines, billboards are constantly before their eyes; radio, movies, television enlist both eye and ear; business methods of advertising, "commercials" and displays compete for willing clients among children as well as adults. Further, commercial recreation with more limited, yet more dangerous appeal offers its powerful stimulus to young people in the form of dance halls, night clubs, liquor, drugs, automobiles, etc.

The time and intensity young people devote to all of these diversions shows that they must fill a definite need not otherwise sufficiently recognized or satisfied.

We have just heard that basic needs demand to be satisfied, and that this satisfaction is the prerequisite for the individual taking the next step in the developmental pattern. This could be more easily achieved were it not for society's insistence that the need be satisfied in a fashion acceptable to its standards. Since the needs of the individual and the needs of society are often diametrically opposed, frustrations must ensue, followed by guilt feelings in the child, hostility and aggressiveness, all of which are naturally also unacceptable to society. Tensions continue to increase between society and the child. Now he's on the skids to become a social outcast! What stops him?

To begin with, it is one of his basic needs, namely, a desire for acceptance and love that turns the tide and, secondly, there should be helpful guidance from the surrounding. As the latter is all too frequently lacking or inadequate, the only way for him to proceed in order to find a solution for conflicts and become an accepted member of society is to use the means at hand in a fashion all his own. Much of the seemingly irrational, silly or aggressive behavior in children is a result of this struggle.

The first thing a child wants and gets from the opportunities offered is excitement and adventure. The modern urban setting offers anything but these to a youngster. Cramped up in a flat or apartment, any noisy activity will not only get in his mother's hair, but will soon bring the neighbors pounding on the ceiling, or the landlord's threats of eviction. Even outside the home there is no place for him to roam. Aside from the dangers lurking in traffic, he soon finds out that the garden with luscious berry bushes, or apple trees with tempting fruit, yes, empty lots, where he builds

himself a secret lair, belong to someone else who rudely and forcefully suggests that he be gone.

What wonder then, if he seeks his adventure vicariously and chooses what best suits his purpose and does not arouse the ire of society! He turns to substitute adventure.

People, old and young, cull from material presented to them those items only which embody a causal relationship with their thoughts and feelings; they ignore or eliminate other items no matter how important they may be to the material itself, for, to be grasped and assimilated, an idea or act, an experience, has to fit into the individual's personal scheme and add to a possible explanation or solution of the problem with which he is wrestling at the time.

Thus, the acts of aggression as presented by printing press, movie screen or air waves do not strike children so much as acts of cruelty and depravity as they offer them a release of their own feelings of aggression, as long as the material presented has a "moral" ending, that is, the villain is punished and virtue conquers. The child, as his needs may require, identifies usually with the hero or the heroine, but he is also able to identify with more than one character at the same time, so that he can clear his guilt feelings by "taking on himself the villain's punishment"; then, switching back again to the hero, he triumphantly overcomes all obstacles.

By far the greater proportion of stories have a "happy ending," thereby serving well the child's needs and society's requirements. The so-called "horrific" subjects have no such value and can do damage to a critically maladjusted child, whereas even the gruesome ones are taken in their stride by normal children, who either think them silly, or simply cannot make use of them as much too far removed from their immediate needs.

The comics, with the exception of a very few, fill all of the child's requirements. There is excitement galore and freedom of action. There are boundless possibilities to overcome the limitations of time and space, of performing the impossible, of finding every wish granted. Moreover, the continuity of the main character facilitates identification. Into this atmosphere are woven the problems of every day life and their solutions worked out. Punishment is usually meted out by magic, as realistic measures would come too close to painful life situations. Death has not the same implication that it has for adults; it is merely a temporary absence, and the dead person reappears at will without further apologies.

Ten to 12 million copies of about 100 different "funny books" are sold per month! This is of the greatest concern to parents, especially the more ambitious ones, who can see in these books nothing but depravity, esthetic and moral, and consequently would wish to see classic literature substituted for them. But it is not a question of substitution—the two trends can and should exist side by side.

Lauretta Bender stated that comic books should be looked upon as the folklore of this age, the equivalent of the mythology and fairy tales of past ages, in which were expressed the social problems of their times, the best having remained vital through the ages, because they have so well expressed basic human problems—just as the comics do now, in form and terms more appropriate to the present age. The good ones have a therapeutic effect; the poor ones which capitalize on snobbishness, race hatred and bigotry should be eliminated.

A survey of stories told spontaneously by children illustrated the fact that children chose the subjects for their stories mainly from personal experience rather than from material gathered from magazines, radio, movies or comics. And some surveys—differing from the survey on movies sponsored by the Payne Fund—have shown that only a small percentage of juvenile delinquencies committed had their root in such fare, rarely even were instigated by it.

One serious drawback is the fact that children will often read these books to the exclusion of physical exercise, fresh air, social contacts and broader impressions. They also develop the habit of being onlookers rather than participants. Absorbed in moderation, the comics may be considered definitely helpful.

Unlike the comics which cater directly to children, the movie and radio scripts are not primarily written for them. Their offerings are very mixed, to say the least, a small number only well suited to the entertainment of the child and to his fantasy life, which R. Griffiths calls the "link between intellect and emotions" and which, as such, is a vitally important factor in emotional growth. By and large, however, movie and radio programs are certainly not helpful.

Normal youngsters will, as stated earlier, skip what does not interest them or does not fill an emotional need; maladjusted children will see their problems emphasized by unsuitable stories, not because of the subject presented, for the real trouble lies in the child himself, but because they re-

inforce instead of helping him to solve his conflicts. Considering that of the 80 million people attending shows every week, one third to two thirds are children, the type of program and attendance merits our attention.

It is rather appalling to learn from a survey made by a League of Nations committee some years ago that the United States of America is one of only three nations in the world that do not have any regulations or laws governing the attendance of minors at movies. What television will have to add to the already heavy dose of "canned" vicarious activities of the radio and movies remains to be seen.

Of the many environmental factors which materially influence the child, the one that perhaps looms largest, most regularly and persistently in his early life is school.

School for most children is not a happy experience. Still in the grip of a tremendously rapid expansion in the endeavor to meet the invasion of "war babies," schools have been occupied with physical and intellectual, rather than emotional and social problems, nor have they had time to train the proper personnel to assist them in broadening their scope. It has been possible only in exceptional cases to introduce into the curriculum progressive methods based on the ever widening knowledge of child psychology. If the dunce cap and the rod are no longer the ubiquitous equipment they used to be, it is probably because of the introduction of more refined methods to reach the same purpose.

Considering that one fourth to one half of the child's waking time is spent in school, one deplores the opportunities missed for developing potentials such as insatiable curiosity, social gregariousness, search for authoritative and tactful guidance.

The development of the public school system and compulsory education in America sprang as much from the democratic idea that all men are created equal and are entitled to equal opportunities, as it did from the optimistic surmise that, given the opportunity to learn, i.e. build up a stock pile of facts, there could be no limit to achievement. Intellect became a fetish and school its temple, with our whole society worshipping at its shrine, in complete disregard of the individual as a whole.

When the curriculum tries to fit a preconceived pattern to an assumed type of individual, regardless of the true personality, and is more bent on training the head than the heart, it has missed its avowed purpose of preparing the child for life, and for future happiness and success.

A hopeful note has been struck by the establishment of nursery schools, which work in close connection with the home, particularly the cooperative nursery school, where parents take an active part in the curriculum. Here not only is attention paid to the child's physical welfare, but he is given ample opportunity for intellectual, emotional and social growth under the supervision of trained personnel, who are also capable of directing parent education.

Supervised recreation by schools and recreation departments, also by private groups like the Scouts, Boys' Clubs, Camp Fire Girls, can be welcomed as one of the most progressive approaches to a beneficial influence on the emotional life of the child. They offer him the stimulation best suited to the respective growth levels and in favorable situations which are likely to protect him from the deleterious influences of commercial recreation and to promote physical, intellectual, emotional and social maturity by teaching him the essentials of responsibility, give and take, good sportsmanship, loyalty, independence and creativeness.

These programs are expensive and, like all preventive work, less apt to fire the donors' imagination and loosen their purse strings than the more influential, advertising commercial groups with their flashy appeal to excitement, sex, dizzy whirl and desire for escape. Such excitement is not constructive, it solves no problems; it merely interferes with emotional growth, inasmuch as it caters exclusively to immature drives and does so to excess.

Factors in the Community—Indirect Influences

There are more subtle influences than the foregoing in the child's environment—I might call them atmospheres, as they unobtrusively, nevertheless powerfully, leave their imprint for life on his emotional attitudes.

These are, at consecutive stages of his development: (1) the child's social relations to other individuals and groups, (2) his political relations to the state and the world, and finally, (3) his relations to the universe.

A narrow minded, egocentric, biased, bigoted, possibly just indifferent atmosphere will hinder

the child's emotional growth, while an open minded, altruistic, tolerant and responsible atmosphere gives the child every chance of developing the best potentials through the use of which he may attain maturity.

Maturity is the culmination point of a growth process.

All growth processes being bound by genetic law to an irreversible sequence, it goes without saying that if the first step—namely, the child's social adjustment to his immediate surrounding—is not realized in his early years to the full extent which that particular level requires, he will remain arrested at that level and fall sadly short of his capacity to become a happy, useful and effective citizen of the world.

The earliest social adjustment in the community is made to playmates. Children are not class or race conscious. They choose for their companions those of their emotional and mental level, regardless of what might amount to a difference of several years in their chronologic age, many inches in their stature, wide variations in color, nationality or creed, or, for that matter, political affiliation.

Discrimination based on any other factor than personal merit is artificially and painstakingly indoctrinated by emotionally immature adults in the environment, who, not able to meet successfully the demands of life incident to their own chronologic level, look around for a scapegoat. Dictated by emotional frustration, this attitude is thoroughly irrational, therefore, brooks no criticism. These attitudes we call "prejudices."

Prejudices are "habits of feeling." Being feelings, they are deep rooted and violent; being habits, they are hard to eradicate. Exposure to prejudices at an age when the child learns and integrates into his personality by feeling rather than by thinking is always fraught with danger. A child reared in a favorable emotional atmosphere will grow up averse to accepting prejudices. He passes his own judgements and makes his own decisions.

Maturity requires an independent spirit, self confidence, a sense of values on which to make choices, a sense of responsibility in which empathy replaces egocentricity, and an affirmation of life expressed in a philosophy or religion embodying in one form or another the "Golden Rule."

How can an individual find a solution for domestic and foreign political problems, if he has never learned to get along with the neighbor boy, if he has been taught to shun people "below his class," and conveniently blame all the evils of the world on "foreigners," the while reserving unto himself the privilege of superiority and all too frequently divine partnership in asserting himself over others for selfish purposes?

And again, how can this divine spirit, or what other term you wish to apply to the absolute force which governs the cosmos, and which is postulated by human beings both emotionally and rationally, ever emerge to the full satisfaction and benefit of individual and race, if it is restricted to the narrowly circumscribed limitations as found in most organized religions, who visualize the spirit as an anthropomorphic being, taking sides in human issues, fairly and unfairly dealing out reward and punishment, and, last but not least, bribable by prayers and promises?

The emotionally mature person senses such an attitude as a desecration of the absolute force. The immature grasp it as a support and steadying influence, only to be too often disillusioned in moments of crisis or even driven to unjustified feelings of confusion and guilt.

The essence of practically all religions contains that core of teaching which contributes to man's best and most complete emotional development; it is the form in which it is clothed that too often obscures the spirit.

Form in itself, just like different customs, manners and looks among peoples, need not become detrimental to the spirit, as long as it does not tamper with and distort the core.

In spite of many attempts by certain religious groups (one of the best known, the Conference of Christians and Jews) in the direction of finding and isolating from the stack of unrelated and irrelevant doctrines a common denominator, progress is delayed by the fear and defensiveness of immature personalities within these groups.

More progressive churches are demonstrating by their greatly increased attendance that psychology and psychiatry are not incompatible with religion, because, where both have joined hands, it has been to the profit of either side.

These same churches also have found an excellent approach to the child, bringing the ethics and the mysticism of religion to the child's level, and creating for him in the Sunday school setting a center for social. emotional and spiritual growth.

One of the greatest handicaps to progess lies in a vicious circle. The environmental influences are man-made—the men who create them are essentially immature—the organizations created by them, of necessity, perpetuate the immature pattern in the next generation—and so on and on.

Where and how do we break this vicious circle?

Environmental Factors in the Home—Economic-Cultural

Our greatest promise of breaking this vicious circle lies in the home.

If, as has been repeatedly stated, emotional maturity can be reached only in a definite sequence of steps, each completed within itself, as the result of the most favorable combination of inner and outer factors, it is without doubt the early and earliest years of life which become of crucial importance. These are spent in the bosom of the family.

The home exerts the first and most insistent influence on the child. Research done on the influence of parents and many other persons upon children's attitudes showed the correlation between child and parent to be higher than the correlation between child and any other influence, the correlation between mother and child rating the highest. The father, in American society, has become more of an "absentee owner and occasional house guest."

The home has been undergoing a radical change in the past 100 years, due primarily to the industrial revolution and factors secondary to it. Compared with the ideal picture of the home as conceived by poets and moralists, even with the optimum set up as visualized by psychiatrists, the modern home can be looked upon as a failure. On the whole, what now stands for a prototype of the modern home is actually lacking in many respects; but is it a complete failure and therefore doomed to disappear, to be supplanted by a better project? No, it is not really a failure in principle. It still is a sound institution, but one going through the crisis of readjustment to a new situation.

As anthropologists accumulate more and more significant findings on human relations to broaden our knowledge of family life, they seem to confirm the conviction—with certain modifications in various localities—that the monogamistic marriage has been considered, and still is, the most practical and constructive form of family life in the development of our civilization.

At the present time the adjustment from the feudal, patriarchal, agrarian set-up to the modern industrially orientated one has been hampered by the prompt assimilation of overt situations, materials and technics, before social thought and organization had time to catch up with them. Outwardly, we fall in with the tempo, the opportunities and the demands of the industrial era, but we still retain in our thinking and feeling the relationships of patriarchal days.

The steady flow of population from the farm to the city, the extension of urban life with its cramped living quarters, with the development of the so-called "proletariat," that knows the desperate uncertainty of jobs, irregularity of pay checks, monotonous, initiative-killing occupation, from which —with the best of intentions—the worker cannot derive much satisfaction of achievement or creativeness, insecurity has crept into the most well ordered household.

The emancipation of women and greatly increased opportunities for them to work outside of the home, also the necessity of their adding to the family budget, brought about a shift in authority from the "pater familias" to the mother as head of the family. The pendulum has swung to the other extreme and it will take time before it once more finds its balance.

In the meantime, the situation in the family, being neither understood nor properly exploited by either parent, both jealous of their prerogatives, offers innumerable occasions for friction, arguments and, finally, complete breakdown of the family. What has been tagged as lack of good will, selfishness, moral turpitude, overbearance are as frequently escape measures as they are causes for such an intolerable state of affairs.

Environmental Factors in the Home—Parental Attitudes

To this economic-cultural crisis is added an aggravating factor, when both parties to the contract marry with the most meager knowledge of sex and with no other preparation than the immature concepts conveyed by the just mentioned environmental influences in their distorted picturing of life situations. The shock of the real situation is often more than the individual can grapple with. Unless other favorable influences have helped him to reach his emotional maturity and make his adjustment, this certainly is not an atmosphere conducive to raising happy, successful, adjusted children.

Dr. Shirley has outlined a schedule of the desirable parent-child relationships and the significant attitudes which combine to bring about the best results. It does not sound too involved or difficult.

A parent of average intelligence can follow, understand and readily accept such a systematic plan; carrying it out is quite another story!

As the parent valiantly tries to follow the course outlined, he finds himself constantly stymied by many a hazard.

To begin with, the inevitable problems of married life take their toll in confusion, irritations and tensions.

Moreover, parents are surrounded by public opinion, mostly of the warped type, hallowed through custom and tradition, and forcibly voiced by neighbors, teachers, friends, ministers, priests and, last but not least, the in-laws. Such well meant advice usually dates back to an era from which we have but recently emerged, a period of trial and error rather than organized research, of superstitution rather than scientific knowledge, and seldom does it prove helpful in solving the problem at hand. The authoritative utterances, however—at least, the traditional authority of the persons making such utterances—overwhelms the parent with shame and guilt feelings because of his inability to make the time-honored methods work.

Only slowly and gradually are we acquiring the insight and consequently the courage to face these authorities with the new knowledge of psychology and psychiatry as applied to human relations.

So far, the school has been too dictatorial, the law too punitive, medicine too paternalistic, business too ruthlessly exploitative and the church too moralistic. A true searching of souls is at hand, and a lot of house cleaning will have to be done, before all environmental influences can join in mapping an effective human relations program.

The greatest of all handicaps to the parents' carrying out a suitable child training schedule is their own immaturity, the tragedy of the vicious circle.

Parents, in their youth, were also exposed to environmental influences, whose object and profit lay in keeping them from growing up, nor was their home atmosphere always the most suitable one. Is it surprising that they should have remained arrested on one of the earlier levels of emotional development?

The parent who, in his childhood, has not known a mother's love and has not, by identification, been able to develop the proper pattern of love, finds himself unable to offer it to his children.

The parent who has been overindulged and overprotected in his youth, remains a helpless, indecisive, inconsistent individual—arrested at the preschool level—looking continually for props, when he should be supplying support to others, and always he remains in deadly terror of the children's aggressiveness.

The parent who has been rejected by his family and has harbored resentment and hostility in response will vent these repressed feelings in childish aggression on his family in turn, and become a domineering, tyrannical, even brutal parent.

The parent, disillusioned in his concept of the overidealized, romantic, blissful marriage, "life on a bed of roses"—an adolescent attitude—will substitute the child for the disappointing mate, lavishing on him and demanding from him an undue amount of permanent attachment and devotion.

A parent who has failed to reach the overambitious goal his parents set for him will frequently later be driven by unresolved guilt feelings to realize this goal through his children, keeping them under constant pressure in his effort to stimulate their ambition, demanding specific work to the exclusion of any other, holding over their heads, in repetition of their parents' pattern, the threat of "ingrate," should they ever show signs of lagging or independent opposition.

All of these attitudes are samples of emotional behavior arrested on various levels of development. They in themselves unavoidably create arrest of emotional dvelopment in the children, and the pattern is perpetuated—not because it is inherited, but because the same type of influences are at work.

Parents do not choose to be "bad" parents. They have the best of intentions, the highest hopes and the most lofty ambitions for their children. All the more do they feel crushed, ashamed and guilty, when nothing but confusion, resentment and aggression are hatched.

I used to think in my youthful intolerance that adults by the age of 25 were calcified beyond hope, and that constructive measures could be applied only to the plastic age of childhood. Experience has enlightened me. Naturally it is more difficult to obtain a change of attitude the longer a certain trend has persisted. It is easier to establish a good habit in the beginning than first to have to uproot an established bad one. Even so, it is not always hopeless.

Where some intelligence is present, when the parent is willing and anxious to submit to treatment for the sake of making a better adjustment, there time, patience and optimism on the part of doctor are justified.

What these parents obviously need is help in growing up. This sounds like a big order and it really is, considering that it sometimes takes many weeks and months, in exceptional cases years, to work through with the parent all developmental stages to full maturity. The latter cases would be wise to enlist the expert assistance of a psychiatrist. Such a step is always a difficult one for the patient to take, and it is usually not taken until a bad situation has finally grown beyond endurance. In many instances one cannot but feel that the crisis might have been averted had some understanding and a helping hand been extended at an earlier stage.

The Pediatrician's Participation

This is where the pediatrician can function quite logically and naturally and helpfully as friend, educator, confessor and counsellor. In his professional routine of preventive procedures like vaccination, diet schedules, general examinations, the care of the new baby is entrusted to him right after birth. At this time the mother is exceedingly receptive to any help that might tide her over this period of insecurity and anxiety incident to the novel task of motherhood.

The pediatrician need not become an expert, but there is such a thing as "psychiatric intelligence."

A few well directed words about the needs and drives of infants and a sympathetic attitude toward problems or conflicts which may be worrying the mother will often open the flood gates of repressed feelings and give the doctor an excellent insight into his patient's troubles.

If the need for communication and sympathy was all that oppressed this mother, and if "by talking things over" with an understanding, authoritative person she is enabled to look at her problem and reach her solution in a more rational way, then much trouble has been nipped in the bud.

Another mother may see in the child a threat to her economic security (in our industrial age, children rate as liabilities—in the patriarchal-agricultural age they were assets). This mother has not awakened to her mature responsibilities. On the other hand, economic resources are vital to her peace of mind so that it might be well to have her seek assistance through the mediation of a family service agency. The pediatrician should familiarize himself with the names of service agencies in his community.

Still another mother rejects the child, feels guilty about it and compensates by overindulgence and overprotectiveness. Before attacking the problem itself, this woman can be put at ease and her anxieties released by a sympathetic listener's uncritical acceptance of her with all her "frailties, faults and failures." It is not necessary to approve of the mistakes she has made (that would only impair the doctor's judgment and authority in her eyes) but accepting them as inevitable behavior due to deeper motives is in itself a therapeutic procedure. It is astounding how quickly a tense person will sometimes relax on being told: do not let us speak in terms of good and bad, right or wrong, fair or unfair, just or unjust—instead, let us look for cause and effect. This clears the air of punitive and moralizing concepts (ethical concepts are, of course, retained); it permits the discussion to flow in an objective atmosphere of empathy (if you will accept this seeming paradox); then only can the parent come to view his problems for what they really are, freed from secondary, irrelevant issues.

The next step will consist in a reshuffling of values, acceptance of responsibilities, formerly resented as too irksome, and with moral support from the doctor, the patient will in time develop the self-confidence needed for independent thought and action. The last step requires that the early attitude of dependence on the doctor give way to independence. The moment the patient tells you graciously that she does not need you any more, she is likely to have reached maturity .

No one demands or expects perfection. Parents must realize that human beings, they themselves no less than their children, have their very definite and numerous limitations (perfection might actually be more difficult to live with than a few imperfections). To accept oneself as well as others, with neither conceit nor indulgence, is a sign of true maturity.

In such a milieu the child has a chance to work out the conflicts incident to growing up. By imitation of and identification with emotionally mature parents the child can, step by step, relinquish his childish attitudes, nor need he resort any longer to childish manifestations to obtain his objectives.

In the prevailing atmosphere he will be less resentful of assuming responsibilities as well as accepting authority, and he will become more willing to control his immediate desires for the sake of more enduring satisfaction later. He will grow in his ability to cooperate, become discriminating and adaptable. He will develop suitable love patterns, so that he may be able to give as well as to receive love on a mature plane. He will live in relative harmony with his conscience and keep anxiety at a minimum.

And last but not least, he will thus have had the opportunity to acquire the habits, security and good taste, which enable him to meet the onslaught of environmental influences with that fine sense of discrimination that allows us to profit from experiences without being overwhelmed by them.

Question: Would you discuss the management of temper tantrums?

Chairman Shirley: When children are thwarted—and they have to be thwarted sometimes—they naturally feel angry and may lose their tempers. The younger they are, the less control they have over their feelings. I do not regard an occasional temper outburst as being abnormal. I doubt if socialization of the child is possible without the child's experiencing considerable frustration and anger at times. And yet, if the child is to become well socialized, he must learn that he cannot control his environment by temper displays. Sometimes the best way to handle a temper tantrum is for the parent to say to the child, "We can't have such behavior in our presence. Papa and mama do not behave that way and if you feel that way you must go to your room. When you can behave differently, you can come back." That method of management has two advantages. First, the child learns that he gains nothing by such behavior. Second, through vigorous physical action he gets rid of his anger. If he has a lot of anger, he has to get rid of it somehow. If, however, a child has frequent and severe temper tantrums, I would feel that something is wrong and that the cause of the trouble should be investigated. I would want to know about the personal relationships within the home: whether the parents are too demanding or too thwarting, whether they are too lenient or inconsistent, whether the child feels he is loved and respected, and whether the parents themselves are unhappy, irritable and explosive. I would also want to know whether the child has enough opportunity for activity suitable to one of his age. Young children have tremendous energy and they must be allowed to let off steam at times.

Chairman Layman: The isolation method does not always work. There are parents who cannot convey the feeling that they love their children, and the children then believe that the parent hates them and wants to get rid of them. I think such parents might come back to you and say that you gave them some very good advice but it didn't work. You would wonder why it didn't work in certain cases, while it did in others, unless you realized that basically, you can do practically anything with a child who is secure; but an insecure child who is not loved reacts differently and needs much greater investigation.

Question: Do you consider the expression of anger in very young children with whom you cannot reason or the temper outbursts in children who are tired, wet, and hungry as real temper tantrums?

Chairman Shirley: No. Almost any child will be irritable, fussy and explosive when he is hungry or fatigued. I think it is then better to ignore the emotional reaction and attack the cause. I think of temper tantrums as being severe anger reactions in which the child loses all self control.

Dr. H. J. Freedman, Boston: I have heard repeated several times this afternoon the question of negativism in children. I think that sometimes we overlook the fact that frequently negativism is not true negativism but is really a form of conformity in relationship of the child to that particular group to which the child happens to belong. Speaking specifically, I should like to ask you this question: If he finds that there is a variance between two problems, one of health and one of conformity, what does a physician do? For example, a child of 13 years of age has a tendency to come down with repeated infections and with the infections she is likely to come down with acute asthma. The asthma interferes with her school and with her sense of well-being. Her parents are quite upset about it and spoke to me about it. One of the problems they had with this child was that she insisted on going to school wearing bobby socks, during the cold months. I spoke to this child. She was not negative to me, she was perfectly cooperative; but when she said, "Dr. Freedman, I would much rather have my acute attacks of asthma than be ridiculed by my girl friends at school," I was stymied. My responsibility, in relationship to the child's health, and my concern for the child's emotional security were at odds and I didn't know what to tell her. What should I have said?

Chairman Layman: I don't think that the bobby socks would have much to do with it. I think

that the asthma attacks may have had another foundation entirely; the bobby socks were the obvious reason but underlying that there were probably other things.

Dr. Freedman: I made a statement that she came down with a respiratory infection and in her weakened condition she was liable to real attacks of asthma. They were not attacks due to emotional disturbances; they were purely bacterial allergies. I felt personally, as did her parents, that the manner in which she dressed herself during these cold days may have made her more susceptible to infection. I don't feel that this asthma has an emotional basis; I still feel that it has a bacterial basis. Dr. Lane has just cured a girl after four years of psychiatric treatment. My only feeling in regard to that is that it is not only the function of the physician to tell people what to do. It is also his function to give them the information that they need so that they might make the decisions themselves thereby helping them to come to their own decisions. There are plenty of people who disagree with that, but I feel it is the thing to do.

Dr. R. A. Moore, Charlotte, N.C.: How do you recognize rejection in a mother, and how do you know it is rejection?

Chairman Shirley: A rejecting mother is likely to be highly critical of her child. Her complaints about him may fill pages and she may have trouble thinking of anything good to say about him. Once in a while a rejecting mother will come right out and admit that she doesn't like her child, that she just can't stand him and that she wants to have him placed somewhere, anywhere. More often, however, the rejecting mother feels guilty about her feelings toward the child and tries to hide them. Sometimes, to cover up the feelings of which she is ashamed, she behaves in an overindulgent and oversolicitous way, usually, however, only to vent her hostility in times of stress. In dealing with a disturbed and defensive mother, it is important to be noncritical, so that she can drop her defenses and talk frankly about her feelings toward her child. One can then be more certain as to what the mother's feelings toward the child really are. Then, too, the mother can more easily face her feelings and begin to decide what she can do about them.

Question: Don't you sometimes get a clue from the history? For that kind of mother tends to fall into all of the coercive possibilities that you offer her. She is the one who will carry out the disciplinary orders of the doctor to the extreme.

Chairman Shirley: Yes, I think that is true.

Dr. J. H. Batzle, Riverside, Calif.: This afternoon the word empathy has been brought into the discussion quite a lot. Isn't that an unattainable ideal? I mean by that, are we not all filled with prejudices and immaturities, and isn't that something we have to fight in ourselves in our role as experts?

Dr. Alma M. Sullivan, New Orleans, La.: A good psychotherapist will watch his own attitude. But the more you know about the subject the more you can be objective.

Chairman Layman: We should try to see things from the other person's point of view, not necessarily with sympathy, but stepping into the other person's shoes, feeling what he feels and thinking what he things. When we do that, we are very sensitive as to what is going on within the patient. Then in our questions we try to get him to reveal himself. If we can get close to the patient, well placed words will help draw him out.

Question: Do you people who are taking this up as a life work sincerely believe that a child's emotional growth reaches a point at birth that a child is susceptible to a rejection relationship to a mother?

Chairman Layman: Yes, I personally think that our emotions express themselves in muscular tensions. If the child does not experience a warm, comfortable feeling in relationship to his mother, it will affect his emotional state.

Question: Couldn't the nurse give the baby that same feeling of comfort?

Chairman Layman: Yes. As long as the child is warm and comfortable on personal contact.

Mrs. W. Young, Salt Lake City: Dr. Layman, you mentioned a child's first cry as perhaps objecting to being born. I have always asked my mothers, "Does your child hold his breath?" You find many children who, at 3, 4 or 5 months old, begin to hold their breath. Do you feel that this is the first chance the child has to show his sense of rebellion or insecurity? Many of these children, I find, go on to have tantrums, persistent bed wetting and food refusal. Is that the time you would try to find the basic principle and is that the first evidence of rebellion that you have in a child?

Chairman Layman: To begin with we do know that there is a relationship between the child

holding his breath and his surrounding influences. I had a mother come to me, whose child was about 6 or 8 years old, and was causing a lot of trouble. She sat there with clenched fists and set jaw and said, "He hated me from the first time they brought him to me to nurse"; of course, it was reversed, she hated him and the minute the child was with her he felt this rejection. That this individual's trouble started very early with the rejection of the child by the mother is very possible; we can't always trace it back that far, unless the mother gives us the facts.

Question: If you expose the mother to the need of her protective relationship immediately after birth when she may be weakened by the process of giving birth, she may have a certain amount of resentment toward the child and therefore reject the child. Why not wait a week or two until she has recovered somewhat from the ordeal of birth? Perhaps then rejection will not have manifested itself.

Chairman Shirley: I believe that most of us in the child guidance field believe that the infant's sense of security depends upon the physical comfort which comes from a warm, personal contact with the mother figure and from the prompt fulfilment of his physical needs. It is my feeling, however, that the effect of rejection the first week or two may be over-emphasized. While the infant may begin to react to it, the significance of the situation is that it may be the beginning of a life-long relationship which gradually but surely warps the child's personality until the pathologic change becomes irreversible. When a mother early shows a marked degree of rejection, she probably needed a lot of help with her feelings before the birth of the child. Certainly she needs help through the well baby and preschool periods if a healthy mother-child relationship is to foster normal emotional development.

Question: Dr. Layman mentioned nursery school. I wonder if you feel that a nursery school can at times cure or at least relieve the situation that has made very severe tension at home. A mother who has just had so much work or so much of her child or children that she is giving all there is to give—do you feel that in a situation like that, having the child out of the house for a half a day will help her to improve?

Dr. Sullivan: The attitudes developed in the home are the most important. A child will carry faulty attitudes to the nursery school and make it very difficult for the teacher. When the trouble at home goes deep, I don't think the nursery school will be much help. The main use of the nursery school is to develop the child's possibilities. I don't think they should go before three years old but they do.

Chairman Shirley: The value of a nursery school for emotionally disturbed children depends considerably on the training and skill of the nursery school teacher. A well adjusted, mature teacher who has had training and experience in dealing with children's emotional problems may do a great deal for a child and contribute greatly to efforts to change the home emotional environment. An untrained teacher may even have trouble with reasonably well adjusted children. There are, of course, children too disturbed emotionally to adjust acceptably in any nursery school, and often much work must be done with the family before an attempt should be made to send the child to school. In regard to the statement about the overburdened mother, when a mother is tied down with several children 24 hours a day, seven days a week, she may indeed lose her perspective. Not infrequently I encourage mothers, if possible, to plan their work so they can have some time with their husbands and for themselves, so they can replenish their supply of equanimity.

Dr. G. R. Alpert, Richmond, Calif.: What do you think of the idea of extending our educational system below the kindergarten to take in the preschool and nursery care centers? There is considerable argument at present about the value of cooperative child care centers, the main argument against being that the child's place is in the home. But as I watch the children in these child care centers, I think it is the greatest thing that could happen to them. They learn to play with other children, and this has a good effect on the child's personality. The aggressive child learns to share his toys, and the personality of the timid child is brought out. It seems to me there is a very definite need in our educational system to extend it to the preschool level and incorporate the cooperative nurseries which are usually only open to working mothers but should be open to other mothers too. I think in the future sufficient nurseries for preschool children will become a reality, particularly in our urban areas.

Dr. H. H. Finlay, Wilkinsburg, Pa.: One of the foremost problems which we as a world face today is how to train people to get along together. The period of life, in my experience at least, when the foundations are laid down for the ability of people to live closely in a cooperative and secure manner is during the first 4 years of growth and development. The most important personal

relationship which the child has during the first 4 years is with the mother, and anything which interferes with that relationship during the first 4 years is going to affect adversely the child's later personal relationships. I think we should not put too much emphasis on the importance of the direct outside social influences on the young child when the important thing is for the child to experience a satisfying and secure relationship within the family pattern. Social development outside the home comes later, and, frankly, I don't think it plays too important a part until the age of 8 or 9. For that reason I question the value to the child of the school situation before the age of 4, though I think the cooperative nurseries have value in parental education.

Dr. R. J. Mason, Birmingham, Mich.: Dr. Layman has extolled the virtues of the comic magazines. I am wondering if all pediatricians as a means of securing better emotional development of their patients should have comic magazines in their waiting rooms?

Chairman Layman: We are unable to keep them out.

Chairman Shirley: I think pediatricians can do a great deal of good by encouraging those groups who are attempting to improve the quality of comics—getting better art and more suitable stories. Comics are here to stay, so why not make something more worth while out of them?

Dr. H. T. Clay, Tacoma, Wash.: Does the modern psychologist let physical punishment enter into his technic at all, or is that nowadays obsolete?

Chairman Shirley: It is my belief that better methods of discipline than physical punishment can usually be found. Good nursery school teachers have found that they can handle even motley groups of children without resorting to physical punishment, and psychologic experiments have shown that physical punishment is an inferior method of discipline. And yet, as physicians dealing with parents, we have to be realistic. In many, if not most homes, there occur emergencies and situations when parents just do not know what else to do but to spank. In many homes, too, emotional tensions between parents and child occasionally mount to the breaking point, and both parent and child may obtain relief from an explosion. When parents ask me about spanking, as they often do in the first interview, I am inclined at first to be somewhat noncommittal, for I feel that if you say "no" to a mother who knows no other method of discipline, you may be only making a bewildered and insecure mother more bewildered and more insecure. It has been my experience, however, that as parents gain understanding of their children's behavior and the role they are playing in their children's lives, physical punishment becomes less and less important to the parents and is usually discontinued. I am quite convinced, also, that when children are suffering from more anxiety or hostility than they can handle, physical punishment is of no benefit and is often distinctly harmful.

Chairman Layman: I would like to give a résumé of a case that I personally observed. I disapprove of corporal punishment. I think it arouses resentment and that nothing is really gained by its use. I think you do get momentary results, yes, because of fear in the child, but you don't build character this way. Now to the case: a woman had wanted a child for a long time, so when she finally adopted one she was extremely indulgent towards him, but at the same time very punitive in her endeavor to train him well. He became a terror. He was considered the worst child in the block. She had to lock him up in the yard for fear of the neighbors' wrath. The household and the child were in a continually upset condition so that there was danger of the child being taken away from her. She was willing to do almost anything to keep him. We went through the whole situation and I explained to her that this child was utterly confused and resentful; that he was getting even with her for the discipline, while testing her; he wanted to see how far he could go without forfeiting her love. I said that maybe ignoring him was best. If she did not get so upset, he would soon give up behavior that did not prove effective, that is, which did not "get a rise" out of her. She didn't come back for weeks and I was getting a little anxious. When she did come back, she seemed calm and happy. I asked her how things were going and she said, "Fine." She reported that she had ignored whatever the child did, even though he continued to upset the home for two solid weeks. Then one day when she felt she had regained her calm after he had been particularly destructive she administered "one sound whack" and he has not been a problem since.

Question: Would you go along with the idea that the child who is sure of the affection of his parents is not really badly damaged by physical punishment?

Chairman Shirley: The child who is sure of his parents' love and is confident of their integrity is not likely to be seriously harmed by an occasional spanking.

Dr. E. L. Timmons, Colorado Springs, Colo.: We did have, 75 and 100 years ago, some pretty good citizens brought up in this country. They developed to be pretty fine men. We didn't follow

too many of the rules we are advocating today. In Dr. Layman's case, do you think that one spank made a cushion out of the young gentleman? I had a case where the child had tantrums. We advised the mother not to pay too much attention to the behavior, but when he gave quite a display of temper in public, the mother gave a long spanking. He became a Christian. He was happy and went along very well. Even though they are spanked, children can understand that parents still love them and want to help them. Instead of feeling increasing resentment against the parent, they can also believe that what they have done is wrong.

Chairman Layman: The most important aspect of this, of course, is consistency. The child has to be sure that he knows what the mother is going to do. It is difficult for an uncertain or emotionally disturbed parent to be consistent, but consistency gives the child a guiding line. He must also learn that the mother means what she says.

Dr. G. F. Weinfeld, Highland Park, Ill.: I wonder if you would comment for a moment on the child's basic needs for prohibition and restraint of his innate aggressiveness in contrast to imposing restraint because of the adult's comfort and convenience.

Chairman Layman: The child has a definite need for guidance and discipline because he is continually being influenced by so many stimuli in his surroundings that he often does not know which way to turn. A small child goes in every direction at once, impulsively. This is not satisfactory either to himself or to society. By giving him guidance and directions in a diplomatic and sensitive way, the child's needs for developing his drives are not completely frustrated, yet he is given the opportunity to also become a fitting member of society. Tactful discipline is an essential factor in developing in the child a true feeling of security.

Chairman Shirley: Much of our difficulty in regard to matters of discipline and punishment are due to our tendency to think in terms of extremes and of either-or. It seems that either we have to go all out for permissiveness or we have to put our faith in strictness and punishment. It is much more realistic and effective to find the proper balance between these two extremes, though the optimum balance varies with the age and temperament of the child. We know that all children need a certain amount of leeway in which they can function on their own, and that their need for independence increases as they grow older. We also know that if unrestrained or unguided, children will frequently overstep the bounds of social tolerance and keep themselves and their parents in hot water. All children need to learn the limits to which they can go in their behavior, and there does, therefore, have to be authority in the home. The child who never learns the meaning of authority in the home is likely to have trouble later in school and in social living. So questions which all parents must answer for each individual child are: "What of my child's behavior should I tolerate; what can I best ignore; when must I put my foot down; and how best can I enforce my demands once I have taken a stand?" These questions are not easy to answer. There are no sure-fire blueprints to go by. Reasonably well adjusted and mature parents will usually find common sense answers to which the child can adjust. Sometimes, however, the counsel of the physician will give the mother better understanding of the child's behavior and needs and thus greater consistency and security in her management of the child.

Dr. Batzle: When a mother asks, "How am I going to punish my child?" I think she is putting the emphasis in the wrong place. I think you should try to think of other things that she can do to avoid it.

Question: Aren't some parents too concerned about conformity?

Chairman Shirley: Too often the parents' primary concern is how to make the child conform to their adult standards. Such parents are bound to have serious difficulties with their children, and they can be helped only if they can be led to accept standards which are compatible with the child's stage of development. But even to the extent that conformity is a desirable goal, it cannot be best or completely obtained through coercion alone. It is the reasonably happy, secure and self-respecting child who can most easily accept limitation and authority. If the parent-child relationships in the home are wholesome ones, the child will, as he is able, gradually accept the standards which the parents themselves observe, not so much because he has to as because he loves his parents and wants to become like them. Sometimes, too, particularly when dealing with adolescents, parents must be encouraged to give their children more independence, so that the children can experiment, learn by experience, and thus grow in skill and self confidence. Not infrequently, much to their parents' consternation, children insist on learning the hard way.

Question: How do you handle a situation where a grandmother insists on doing everything for

the child and won't let the mother do anything and as a result the mother says that she has no discipline over the child because the grandmother always steps in. Is it better to discuss the problem with both of them or with each of them individually?

Chairman Shirley: There may be situations of that kind in which a three-cornered interview with grandmother, mother and physician can result in benefit, but it is my feeling that ordinarily it is better to interview the two separately. In the situation you described, there is likely to be more or less deep-seated emotional or personality difficulties in either the grandmother or the mother or both —a grandmother, for instance, whose sense of security depends upon her ability to dominate her daughter, or a mother who has never grown up emotionally. When there is tension between the two, it is easier for each to talk freely about her own feelings in private, and it is thus easier to give each the individual help she needs.

Dr. J. K. Calvin, Chicago, Ill.: Do the races that are very affectionate with their children have behavior disturbances in their children, or are the serious problems largely limited to those people who are relatively cold, such as perhaps the northern races? Also, could you give us some idea as to how to avoid conflicts in the child about 1 year of age who gets into everything?

Chairman Shirley: Modern anthropologists have accumulated considerable evidence of the importance of early child care in both the character structure of the individuals of a tribe and the cultural patterns of the tribe itself. I have just been reading Ruth Benedict's comparison of the cultural characteristics of the Zuñi Indians of New Mexico with those of the Dobuans of Melanesia. It is astounding, when you stop to think of it, what different types of people can be made by cultural forces from, in all probability, the same kind of raw human material. The Zuñi Indians, on the one hand, were restrained, mild-mannered and peaceable whereas the Dobuans, on the other, were morose, suspicious, treacherous and cruel. One anthropologist has recently said that our knowledge of the relationship of child care to the development of personality structure is one of the greatest discoveries of modern times and that, whether we realize it or not, in scientific knowledge of personality development, we have in our hands the key to future human evolution.

Chairman Layman: Interest in cultural influences is gradually coming to the fore. The anthropologists' research among primitive peoples and investigations done in cities like New York and San Francisco where we have a population of many cultured background have demonstrated the effect of different cultures on the ways of bringing up children. For instance, in Chinese culture, when a child misbehaves it reflects on the whole family; every family member is, therefore, eager to help prevent trouble or remedy it when it occurs. The Japanese, with their rigid code of behavior, proved to be our best citizens; Japanese children practically never turned up in Juvenile Court.

Chairman Shirley: In regard to the question about what to do with a child of one year who gets into everything, I think one important thing the pediatrician can do is to forewarn the parents that such a situation is bound to occur and is perfectly normal. The one year old child is full of energy. He is interested in the world about him and is driven to explore and investigate. As yet, of course, he has little judgment, no sense of value and no feelings of right and wrong, so he does have to be diverted frequently, restrained at times, and thus protected by his parents. Yet he needs an opportunity to learn by experience about his capacities and limitations as well as about the material world. I think it is wise to keep valuable, destructible things out of his reach in infancy, but as he grows able, of course, he must gradually learn to respect adult values. A constructive management of the problem requires patience, persistence, common sense and no little sense of humor. There are two extremes of attitude which parents should be helped to avoid. One is for the parents to be uncertain, anxious and overly submissive, allowing the child to gain the upper hand and to dominate the household. The other is for them to come down on the child like a ton of bricks and thus to scare him out of a few years' emotional growth.

Question: What advice do you give the mother of an 18 month old or 2 year old child who won't stay in bed?

Chairman Shirley: My advice would depend upon my evaluation of the total situation. I would want to know about the child's health, the sleeping arrangements, the child's general adjustment, and the emotional relationship between the child and the mother. If I think that the child is healthy and happy and that his relationship with the mother is a reasonably good one, I am inclined to suggest that the mother try being firm about it, letting him fuss a while—until he learns that his mother means what she says. I have also on occasion suggested that the mother ignore the child and make his experience while up as boring as possible. That has worked in a few instances. But if I

think a child is unhappy or afraid, I think the important part of treatment is to try to change the child's feelings.

Comment: Many mothers ask what to do about this behavior or that, but these questions cannot be answered without a knowledge of the background.

Chairman Shirley: I recall a boy of 3 years who woke up in the middle of the night and from then on either kept his mother coming to his bed or insisted on getting in bed with her. There were other symptoms of anxiety, however, and there was gradually revealed a whole series of incidents which made the child feel highly neglected and unloved. When the mother understood the situation, she was able to handle it constructively and within two weeks the trouble at night had cleared.

Dr. P. E. Williams, Hamilton, Ontario, Canada: When we have children who insist on getting up and walking around at night we use restraint jackets for a week or so and they stop doing it. Is that good therapy?

Chairman Shirley: I suppose it might work sometimes; I haven't tried it. In cases in which the children are suffering from profound anxiety or resentment, I would keep in mind the possibility that the method might increase the emotional disturbance.

Dr. Finlay: I think that sleep is like appetite in that we can put more confidence in the child's judgment than we used to think. Children have a natural need for a certain amount of sleep, though the amount varies from child to child, and by and large they will get the amount they need. If there is a happy and contented relationship between parents and child, there are not going to be any more sleep difficulties than there are eating difficulties. If the mother is uninformed, anxious and compulsive, and if she is upset by a lot of the things children normally do, of course she is going to have sleep difficulties. If, when the mother puts the child to bed, he is allowed to play around while she goes out of the room and pays no attention to him, most children, I would say, will go to sleep. The point is, we have overemphasized the importance of sleep in children, and especially that of the nap after the latter part of the third or fourth year. When overanxious parents attempt to force sleep, the battle is on.

Dr. Pauline George Stitt, Honolulu, Hawaii: Don't you think that one of the commonest problems is that mothers are confused about sleep and rest? The mother is aware that in her own life she gets a great deal of rest—or tries to get it—which doesn't necessarily consist of sleep, but she feels that if the child does not sleep, he is not getting any kind of rest at all. If he doesn't sleep at the nap period, she feels it is a lost cause. Then another thing that comes up commonly is that sleep disturbances in the child interfere with the mother's rest. When the mother gets rest for herself or recoups her emotional state by encouraging long naps during the day, she is disconcerted when nights are turned into days.

CONGENITAL ANOMALIES

A Symposium

HERBERT C. MILLER, M.D., *Chairman*

SCOPE AND INCIDENCE OF CONGENITAL ABNORMALITIES

HERBERT C. MILLER, M.D.
Professor of Pediatrics, University of Kansas School of Medicine, Kansas City, Kan.

ANOMALIES OF GENETIC ORIGIN

PROF. CURT STERN
Department of Zoology, University of California, San Francisco, Calif.

MENTAL DEFICIENCIES DUE TO PRENATALLY DETERMINED FACTORS

HERMAN YANNET, M.D.
Medical Director, Southbury Training School, Southbury, Conn.

CONGENITAL MALFORMATIONS INDUCED BY NUTRITIONAL DISTURBANCES OF THE EMBRYO

JOSEF WARKANY, M.D.
Children's Hospital Research Foundation, Cincinnati, Ohio

Presented at the Annual Meeting of the American Academy of Pediatrics, San Francisco, Calif., Nov. 14-17, 1949.

SCOPE AND INCIDENCE OF CONGENITAL ABNORMALITIES

HERBERT C. MILLER, M.D.

PART I. SCOPE OF THE PROBLEM

The purpose of this Symposium is to survey an area of human existence that has interested laymen as well as physicians for centuries, but one in which very few facts have been assembled until modern times. It is only recently that the power of "the foul fiend Flibbertigibbet, who squints the eye and makes the harelip," has diminished and that "the craft and subtlety of the Devil" in the production of monsters has waned. So much progress has been made within the past decade that we now can begin to discuss the problem of the congenitally defective infant in terms of prevention and not just of theoretic eugenics.

While the title of this Symposium is "Congenital Anomalies," it would be remiss to limit our attention solely to anatomic abnormalities. It is becoming increasingly clear that the latter are but one aspect of a much larger problem, namely, the general health of the fetus. The etiologic agents which are responsible for anatomic malformations apparently are capable of producing other types of injury in the fetus. For instance, congenital toxoplasmosis is sometimes associated with microphthalmia, an easily recognized anatomic malformation, as well as encephalitis, chorioretinitis and uveitis in the same individual. It is also apparent that a single anomaly can result from any one of several prenatal factors. Microphthalmia can result from congenital toxoplasmosis, maternal rubella or a genetic factor. Microcephaly is the result of such diverse factors as maternal rubella, excessive exposure to X-rays or a genetic factor. It is evident that a multiplicity of prenatal factors are associated with various morbid states in the fetus, of which congenital malformation is only one. Hence, this Symposium will be concerned with presenting some of the recent additions to our knowledge of the adverse effects of prenatal factors on the human organism and not just congenital malformations.

It is also desirable to obtain a quantitative estimate of the extent to which the health of the population is jeopardized by prenatal factors. This is not easy, as the answer to this question varies considerably with the age of the individual. Many will have died before gestation has advanced more than a few months. Judging from Mall's work, the incidence of malformations in very young fetuses is high. He found 163 abnormal embryos in a group of 434 that he examined.[1] Studies made on the newborn population in European clinics indicate that 2% of newborn infants have anatomic malformations.[2,3] A considerable number of these fail to survive the neonatal period. This does not include those that are sick and die in the neonatal period because of such prenatal factors as isoimmunisation, maternal diabetes or the maternal prediabetic state, syphilis and other prenatal causes. In addition, there is a large group of individuals whose prenatally determined defects and diseases are undiagnosable at that early age, such as those with lesions of the brain and spinal cord, viscera and special sense organs.

Even though it does not yield a complete answer, some concept of the importance of prenatal factors can be gained from a study of newborn infants. No reports comparable to those made in European clinics are available in the American literature. Hence, an investigation was made of the incidence of congenitally determined defects and diseases in the newborn population at the Univer-

TABLE I

INCIDENCE OF CONGENITALLY DISEASED AND DEFECTIVE NEWBORN INFANTS

	Births	Diseased* Infants	Defective Infants	Total No.	Total %
Stillborn	64	9	4	13	20.0
Neonatal Deaths	68	9	15	24	36.8
Surviving Infants	3963	5	47	52	1.3
Total	4095	23	66	89	2.2

* Syphilis, Rh sensitization and maternal diabetes.

sity of Kansas Medical Center. The histories were reviewed of all infants weighing 1000 gm. or more and born from 1944 to 1948, inclusively, who were diagnosed as having any defect or disease state. There were 4095 consecutive births including stillbirths and 89 of these or 2.2% were found to have either congenital malformations or disease states caused by maternal syphilis, diabetes or isoimmunisation. As shown in Table I, 20% of the stillborn infants, 36.8% of the neonatal deaths and 1.3% of the surviving infants were either congenitally defective or had some disease related to prenatal conditions in the mother. It is possible the incidences would have been higher had all 4095 records been reviewed and not just those that were diagnosed and indexed in the hospital files as being defective or diseased. Most of the 89 infants had some congenital defect; there were only 23 of the 89 who had either congenital syphilis, erythroblastosis fetalis or were born to a diabetic mother as compared to 66 who had congenital defects. According to Table II the incidences of

TABLE II

INCIDENCE OF CONGENITALLY DISEASED AND DEFECTIVE NEWBORN INFANTS ACCORDING TO BIRTH WEIGHTS

	Births	Diseased Infants		Defective Infants		Total	
		No.	%	No.	%	No.	%
Premature	383	10	2.6	17	4.4	27	7.0
Full Term	3712	13	0.3	49	1.3	62	1.6

congenitally determined diseases and defects were both higher in premature infants than in full term infants, totaling 7% in premature infants and 1.6% in full term infants. It is seen in Table III that more white infants had prenatally determined diseases than did the Negro infants, largely because there were more white infants who had erythroblastosis fetalis. The incidence of congenital malformations was about the same in the two races. However, 16 of the 36 Negro infants with anomalies had supernumerary fingers. If only severe malformations were considered, the white infants had a higher incidence of these. Anomalies of the CNS were not as frequent as those involving the

TABLE III

INCIDENCE OF CONGENITALLY DISEASED AND DEFECTIVE NEWBORN INFANTS ACCORDING TO RACE

Race	Births†	Diseased Infants	Defective Infants	Total	
				No.	%
White	2052	15	30	45	2.0
Negro	2043	8	36*	44	2.2

* 16 had supernumerary fingers.

† Including stillbirths.

extremities, but were far more serious. Supernumerary digits accounted for almost all of the orthopedic anomalies. Those of the CNS included anencephaly, hydrocephaly, spina bifida, encephalocele and meningocele. There were 17 such infants and 13 died or were stillborn (Table IV). The high incidence of CNS defects in this study corroborates the findings in other clinics[2,3] and is reminiscent of the high incidence of similar defects found by Mall in his investigation of 163 abnormal embryos.

PART II. ROLE OF MATERNAL INFECTION

Maternal infection has long been recognized as a cause of fetal morbidity and mortality. Severe infections in the mother, such as pneumonia or typhoid fever, have frequently resulted in abortion and stillbirth. Even mild infections like rubella are associated with an increased number of fetal

TABLE IV

NUMBER AND TYPES OF PRENATALLY DETERMINED DISEASE AND DEFECTS IN 4095 NEWBORN INFANTS

	Born	Died
	Congenital Defects	
CNS	17	13
Orthopedic	21	0
G.U.	6	0
Cleft Palate	3	0
Miscellaneous	19	6
	Congenitally Determined Diseases	
Rh Sensitization	10	7
Maternal Diabetes	8	8
Syphilis	5	3

deaths. It is not known in these instances whether the fetus dies as a result of a direct extension of the maternal infection across the placenta or in some other manner. Placental transmission of maternal infection occurs, but except for syphilis and toxoplasmosis, the number of proved reported cases are few.

The main interest at the moment is focused on the role of maternal infections in the production of malformations. Gregg's discovery of the effect of maternal rubella on the fetus has been repeatedly confirmed in many lands. The only other maternal infection for which a good case can be made out is toxoplasmosis. Some of the newborn infants with congenital toxoplasmosis are known to have microphthalmia.

Case reports of other maternal infections and their possible role in fetal abnormalities continue to be few, which probably indicates that rubella with more than 1000 cases reported in the literature is a far more prevalent disease after 15 years of age than the other common infections of childhood. The effects of other maternal infections are summarized in Table V. These include those published in a previous summary[4] plus 9 additional cases that have subsequently been reported to the Committee on Congenital Malformations of the American Academy of Pediatrics. A total of 16 defective children out of a total of 86 exposed to various specific infections are recorded in Table V. Seven of the children had congenital anomalies of the heart; there were 10 other defects found, including mental deficiency, pyloric stenosis, harelip, genu valgum, imperforate anus, absent auditory meatus, hypospadias, corneal opacities, club foot and cataracts; none of these occurred more than once except cataracts, which were observed in 2 children. It is difficult to know whether the incidence of

TABLE V

INCIDENCE OF DEFECTIVE INFANTS FOLLOWING MATERNAL INFECTIONS IN EARLY PREGNANCY

Maternal Infection	1st 4 mo. of Pregnancy	
	Exposed Infants	Defective Infants
Rubeola	13	4
Epidemic Parotitis	24	6
Varicella	7	1
Infectious Mononucleosis	6	3
Poliomyelitis	36	2
Total	86	16

defects recorded in Table V is a significant observation, because the method of collecting data favored the reporting of defective children as compared to those who escaped. The number of fetuses exposed to any one of the several infections listed in Table V is too small to warrant any conclusions being made. Taken at their face value, the incidence of defective fetuses is higher than is to be expected in the general population.

Ingalls and Davies[5] have suggested that specific infections like rubella and mumps as well as nonspecific infections like "flu" and "grippe" may be factors in some cases of mongolism. Levy and Perry[6] in a subsequent controlled study could find no supporting evidence for this suggestion. There is no positive evidence that maternal infections of nonspecific etiology have any effect on the fetus. Considerable difficulty will be encountered in establishing the relationship of upper respiratory infections to congenital defects, because the former are so ubiquitous and their etiology so variable. The experimental work of Hamburger and Habel[7] on the effects of influenza. A virus on the chick embryo, showing that anomalies can be induced in the 48 hour embryo, indicates that efforts should continue to be made to determine the effect of specific respiratory viruses on the human fetus. No evidence exists yet that maternal infections of bacterial origin have any role in the production of congenital defects. Continued efforts are also warranted in attempting to establish one way or the other the role of bacterial infections in the production of malformations.

There are several important questions that remain to be settled concerning maternal rubella, mainly, the risk to the fetal population, the period of risk, the epidemiology of the disease and methods of prevention.

Qualitatively the risk to the fetus has been well documented, but the question still remains as to how often the fetus may be expected to escape injury. There are four separate studies which have sought to determine the risk to the fetal population quantitatively.[8–11] These four studies taken together have surveyed a total population of over 32,000 individuals with the results shown in Table VI. About 40% of the fetuses whose mothers contracted maternal rubella in the first trimester

TABLE VI

INCIDENCE OF DEFECTIVE INFANTS FOLLOWING MATERNAL RUBELLA*

	Cases of Rubella	Defective Infants	
		No.	%
Total	331	68	20
1st Tri.	110	41	37

* 1. Fox and Bortin, 2. Aycock and Ingalls, 3. Ober et al. and 4. Patrick.

of pregnancy were born with congenital defects. This does not include abortions or stillbirths. These results cannot be taken as definitive, because the data were largely collected by questionnaires, which preclude careful controls, but they do offer the best estimate of a quantitative answer that is to be had at present.

It seems clear that the fetus is susceptible to injury by the rubella virus during the first 3 months of pregnancy. It is not certain that the same can be said for fetuses who are older. Data collected on questionnaires indicate that some fetuses are injured in the 4th and subsequent months of pregnancy, but these data can not be taken at face value, since the mother's estimate as to the length of her pregnancy and her remembrance of past events are susceptible to error. In a recent report involving 200 cases of rubella in pregnancy there was a considerable lessening of defects in the 2nd and 3rd trimesters of pregnancy if the diagnosis of rubella had been established by an examination made by a physician at the time of the infection rather than from a history obtained from the mother months or years after the event.[4] The latter method has been the one predominantly used in most studies and the accuracy of the data in respect to the exact time of maternal infection must necessarily remain in doubt. From an embryologic point of view it would appear unlikely that the defects attributed to maternal rubella could occur after the 13th week of gestation.

The epidemiology of rubella has assumed a position of prime importance since Gregg's discovery. It is not at all beyond a possibility that rubella, as a result of its effect on the fetus, may turn out to be a more destructive disease than some of the other common infectious diseases of children.

Studies by Aycock and Ingalls[11] suggest that rubella has an epidemiologic pattern like that of rubeola. They found that over a period of 30 years in Massachusetts rubella had a sharp rise in incidence each year in the late winter and early spring months and that there were unusually high peaks of incidence about every 8 or 10 years. Data collected on the birthdates of infants whose mothers had rubella in the first trimester of pregnancy over a period of years in the United States substantiate the high incidence of rubella in the spring.[4] These same data suggest that rubella occurs simultaneously in many parts of the United States in seasonal fashion and, taken together with studies by Fox and Bortin[10] and Aycock and Ingalls,[11] they indicate that rubella reached epidemic proportions in several parts of the United States in the spring of 1943. Judging from previous records, another pandemic of rubella is to be expected in the next 3 years.

Although the reporting of rubella cases throughout the United States has been poor in comparison to other common infections of childhood, there is suggestive evidence that rubella, like mumps, has a relatively high attack rate in the young adult population. The reported incidence of rubella in children under 15 years of age is considerably less than that for epidemic parotitis, varicella, rubeola and pertussis.[12] If this proves to be correct, then it is altogether likely that the adult population contains a relatively larger number of susceptible persons. So far, no satisfactory means has been found to protect the adult population from rubella. Until such means are available, it is to be hoped that as many girls as possible will contract the disease during childhood.

References

1. Mall, F. P., Study of causes underlying origin of human monsters, J. Morphol. **19**:1, 1908.
2. Malpas, P., Incidence of human malformations and significance of changes in maternal environment in their causation, J. Obst. & Gynaec. Brit. Emp. **44**:434, 1937.
3. Landtman, B., On relationship between material conditions during pregnancy and congenital malformations, Arch. Dis. Child. **23**:237, 1948.
4. Miller, H. C., and others, Study of relation of congenital malformations to maternal rubella and other infections: Preliminary report, PEDIATRICS **3**:259, 1949.
5. Ingalls, T. H., and Davies, J. A. V., Mongolism following intercurrent infectious disease in pregnancy, New England J. Med. **236**:437, 1947.
6. Levy, S., and Perry, H. A., Role of maternal illness during pregnancy in etiology of mongolism, Am. J. Ment. Deficiency **53**:2, 1948.
7. Hamburger, V., and Habel, K., Teratogenetic and lethal effects of influenza-A and mumps viruses on early chick embryos, Proc. Soc. Exper. Biol. & Med. **66**:608, 1947.
8. Ober, R. E., Horton, R. J. M., and Fermster, R. F., Congenital defects in year of epidemic rubella, Am. J. Pub. Health **37**:1328, 1947.
9. Patrick, P. R., Report of survey of children born in 1941 with reference to congenital abnormalities arising from maternal rubella, M. J. Australia **14**:421, 1948.
10. Fox, M. J., and Bortin, M. M., Rubella in pregnancy causing malformations in newborn, J.A.M.A. **130**:568, 1946.
11. Aycock, W. L., and Ingalls, T. H., Maternal disease as principle in epidemiology of congenital anomalies, Am. J. M. Sc. **212**:366, 1946.
12. Occurrence of whooping cough, chicken pox, mumps, measles and german measles in 200,000 surveyed families in 28 large cities, Special study series, No. 1, Division of Public Health Methods, National Institute of Health, U. S. Public Health Service, Washington, 1942.

ANOMALIES OF GENETIC ORIGIN

PROF. CURT STERN

In a hospital, among many normal children, a few abnormal ones were born: a brachydactylous child with shortened fingers; an 11-fingered polydactyl; an albino; a child with severe lethal multiple telangiectasia; another with clubfoot; one with pyloric stenosis; a chondrodystrophic dwarf.

In each of these cases the physician is concerned, among others, with two main questions: What was the cause of the anomaly? What is the prospect of its reappearance, in future pregnancies of the mother, in the offspring of relatives of the afflicted child and, a generation later, in the prospective descendants of the now infant?

Let us consider the various conditions from the point of view of the human geneticist and attempt to answer these questions.

Brachydactyly is an anomaly well known to the geneticist from the study of many pedigrees. Typically, it appears in about one half the offspring of a parent who possesses the trait. It is caused by a dominant gene. An affected parent transmits to one half of his germ cells the abnormal gene, to the other half a normal gene; his usually normal spouse transmits to all his germ cells a normal gene. Thus, two possibilities of fertilization exist, joining abnormal gene with normal, and normal with normal. The first type of fertilization leads to the appearance of the congenital abnormality, the second to a normal child. The cause of the abnormality is the presence of an abnormal gene.

Brachydactyly represents what physicians often consider a "hereditary" trait *par excellence*. One parent of the affected child will be found to be affected himself, one of the affected parent's parents was affected and so on in the ancestry, as long as reliable data are available in the family's pedigree. The prognosis for future births is simple. There is one chance in two for each future pregnancy of the mother to result in a normal child, and one in two to result in another abnormal one. There is no chance for the anomaly to appear among the children of any of the normal relatives of the anomalous child. Even his own brothers and sisters, his "sibs," if normal, have the same good prospects of having normal handed offspring as unrelated persons who do not have an affected parent and sib. On the other hand there is again a 50% chance for each future offspring of the newborn baby to be abnormal.

The genetic aspects of the *polydactylous* child are similar to that of the brachydactylous but an important additional feature confronts us. In many families, one of the parents of the affected child again will prove to show the trait and to have inherited it from an affected parent. Often, however, there will not appear an unbroken chain of polydactylous ancestors. Both parents of the anomalous child may prove to have normal hands and feet and so may all grandparents. Yet, other close relatives of the baby might be polydactylous as, for instance, some of his brothers and sisters and some of his uncles and aunts and cousins. The principle of dominant inheritance still holds in these families with polydactyly, that is, of transmittance of an abnormal determiner, an abnormal gene, by one parent and that of a normal gene by the other. The new feature is this: While fertilized eggs endowed with an abnormal and one normal gene are liable to develop the abnormal trait, only some eggs actually do. Others, in spite of their abnormal genic content develop hands and feet with the normal numbers of fingers and toes. The effect of the abnormal genetic constitution does not, so to say, penetrate to the surface of visibility. While penetrance is complete in brachydactyly, it is incomplete in polydactyly.

Incomplete penetrance is a frequent genetic phenomenon. All gradations are known from the complete penetrance of brachydactyly through relatively high penetrance in polydactyly to very low penetrance of genotypes. With low penetrance only a few per cent or even a fraction of 1% of the individuals which possess the genetic constitution that may lead to an abnormality will actually possess the abnormal trait.

The causes for this variability in effect are of various nature. Sometimes an abnormal make-up in one pair of genes will express itself visibly only when some specific genes among the rest of the genotype permit or facilitate expression. Sometimes, nongenic factors play a role. This is illustrated by our 11 fingered baby. The cells which make up his 5 fingered hand are genetically identical with those which form his 6 fingered hand. The different course which the development of the 2 hands took must have been due to slight accidental differences in the circumstances under which the 2 hands of the same fetus were formed. The abnormal genotype is such that it responds developmentally either by normal or abnormal differentiation of the embryonic limb buds.

Genetic prognosis for polydactyly is less concise than for brachydactyly. Instead of a 50:50 chance for normal versus abnormal future births of the mother or of the future children of the baby the chance for normal appearance is increased by a factor which designates the frequency of lack of penetrance. This improved prospect for the mother and the affected child is unfortunately counterbalanced by lessened prospects for the progeny of his normal appearing brothers or sisters. Some of them may be genetically normal and therefore expect normal offspring only, but others, indistinguishable from the former, may be genetically abnormal, nonpenetrant individuals and therefore may have abnormal children.

The *albino* infant, in the overwhelming majority of cases, will have normal, nonalbino parents and all his earlier ancestors and relatives will probably be normally pigmented. Only among his sibs, if he has any, there may be one or more additional albinos. A genetic analysis shows that recessive

inheritance is involved: an albino is an individual whose two parents contributed each an abnormal gene for albinism. The parents themselves are normal appearing since they carry one albino and one normal gene and normality here is dominant over abnormality. Half of the parents' germ cells contain the albino and the other half the normal gene. Therefore, there is 1 chance in 4 that an egg with the albino gene and a sperm of the same constitution will meet. When this happens, an albino child results.

The genetic prognosis is simple. Any further conceptions involving the parents of the albino again have a one quarter chance of resulting in albinos—and a three quarter chance of leading to normal pigmentation. Strangely enough the prospects for future offspring of the albino himself are more favorable than for the further offspring of his nonalbino parents. When the albino marries, his spouse, most likely, will be not only a nonalbino but genetically free from albinism. Thus, all their children will receive a normal gene from the normal parent in addition to the albino gene from the albino parent. They will, therefore, appear normal like their albinism-carrying grandparents. Usually, therefore, albinism occurs "sporadically" or "familiarly" in one generation and not for generations before and after.

The number of normal appearing carriers of a recessive anomaly is often hundreds of times greater than that of the abnormals. Unknown to us, most if not all of us carry one or more recessive abnormal genes which we inherited through many generations from a line of ancestors who also could not be aware of their genotype. By good fortune, they and we usually marry a spouse who will bring to one offspring the normal counterpart of our abnormal gene (while we bring in the normal counterpart of some other abnormal gene which our spouses transmit). But, occasionally, two normal individuals marry who carry the same abnormal gene, and then an abnormal child may be born.

When it was stated above that the prospects for the future offspring of the albino are good we have now to add a word of caution. They are good if he marries someone in the general population, but much less so if he marries a close relative. It can be shown that even a normal appearing first cousin of the albino has 1 chance out of 4 to have inherited an albino gene from 1 of the 2 grandparents whom the albino and his cousin have in common. Consequently the appearance of albino offspring in such a cousin marriage is relatively frequent.

Even the birth of the first albino child from only normal ancestors is often the result of consanguinity. In such cases the possession of one albino gene by both normal parents may be traced to a common ancestor. The chance of a random spouse carrying the same anomalous genes as we ourselves is small, but the chance of a closely related spouse carrying them is by no means negligible. Consanguinity, therefore, involves an increased hazard over that from nonconsanguinous marriages in respect to the hoped-for normality of offspring, even when no unfavorable recessive traits are known in the ancestry. It is not argued, however, that the increased hazard is sufficient to warrant advice against all marriages between close relatives.

The infant with *lethal multiple telangiectasia* is another example of inheritance in which both parents must contribute an abnormal gene to bring about the anomaly. Its sporadic or familiar appearance is like that of albinism with the added part that the inherent lethality of the trait makes it obviously impossible ever to have occurred in the direct line of descent of the afflicted individual. In multiple telangiectasia, however, carriers with one abnormal and one normal gene are distinguishable from persons with two normal genes. The carriers exhibit the more typical, nonlethal form of the trait. The gene is dominant as far as its slight effect is concerned but a recessive in regard to its lethal anomalous action. It is likely that this situation is representative of other inherited traits: in single dose a gene may lead to a slight effect, in double dose to an unfortunate anomaly. Cause of the lethal anomaly and prognosis for future births are similar to those in albinism, but the visible expression in carriers of the slight anomaly is helpful in distinguishing between the carriers and persons free from even a single dose of the abnormal gene.

The appearance of congenital *clubfoot* from normal parents was formerly usually attributed to some accident of intrauterine life, as, for instance, strangulations by the umbilical cord or amnion strings. Newer analysis suggests strongly a genetic basis of the anomaly. Why is the risk of an affected child being born about 36 times greater if one child with clubfoot has been produced than it is in sibships without an affected child? Why is the chance that the nonidentical twin sib of an affected twin has clubfoot no greater than that of an ordinary sib, but the chance of the identical twin sib of an affected twin having clubfoot more than 10 times as large? While it is not impossible to

explain these facts by assumptions concerning the involvement of intrauterine accidents it seems more likely that specific genetic constitutions are responsible for congenital clubfoot.

This genetic interpretation has to make use of the concept of incomplete penetrance. If only some 30% of identical twin sibs of a clubfooted twin possess clubfoot then the identical genotype of the twins must be regarded as only 30% penetrant. In contrast to the incomplete penetrance in the dominantly inherited polydactyly the incomplete penetrance in clubfoot concerns a recessive genotype. This follows from the fact that, as in albinism and in contrast to polydactyly, both parents of children with congenital clubfoot are much more frequently normal than the sibs of these children. Prognosis for future births in regard to clubfoot must obviously be based on joint consideration of the phenomena of recessive inheritance and incomplete penetrance.

Likely, the child with *pyloric stenosis* came from a relatively older mother, since statistics show an increase in the frequency of this anomaly with increasing age of the mother. This shows clearly that a nongenetic agent is an element in the causation of this anomaly—for the genes which the mother possesses and transmits to the offspring are the same when she is young as when she is older. Does this exclude the participation of genetic causes? The answer is negative. Even in the appearance of this anomaly specific genes seem involved. This is strongly suggested by the fact that cousin marriages among the parents of children with congenital pyloric stenosis are considerably more frequent than in the population at large. This increased frequency of consanguinity is, as we have seen, typical for recessive traits, since these traits appear mostly in children whose parents both are normal carriers; and the chance that they are carriers is increased when they are closely related. In pyloric stenosis, as in some other congenital anomalies whose frequency is correlated with maternal age, we observe an interesting interaction between the genetic constitution of the fetus and the variable intrauterine environment provided by mothers of different ages. The penetrance of the child's genotype is low when he develops in a younger, higher when in an older mother. The cause of this anomaly is thus a combination of genetic and environmental factors. It is a situation providing a peculiar inducement to research which has as its goal the control of the environment so that expression of the anomalous genotype is made impossible.

When, in this discussion, the role of genetic factors has been stressed it is by no means implied that there may not be in other instances overriding environmental agents which may lead to abnormalities regardless of the genotype of the developing embryo. It is likely that many of the congenital abnormalities which are caused by heavy irradiation with x-rays of pregnant women will occur in children of any genetic constitution. The same may be true for the various congenital anomalies met in consequence of maternal rubella or maternal nutritional deficiencies. Even in these instances the participation of predisposing genes is not excluded. When it is remembered that the once generally accepted purely environmental interpretation of tuberculosis has given way to analysis which proved the important role of genetic factors in susceptibility to tubercular infection, then it will remain a problem worthy of attention to study whether the effect of external agents on the causation of congenital abnormalities often is only possible on the basis of specifically susceptive genotypes.

Let us discuss the last named of the abnormal infants in the hospital, the *chondrodystrophic dwarf*. Pedigree studies have shown that such a dwarf transmits his trait in typical dominant and fully penetrant fashion to further generations. We would expect therefore that one of the parents of the chondrodystrophic infant is a dwarf himself. In spite of this expectation there is some likelihood that both parents and all former ancestors were normal sized individuals. Indeed the study of pedigrees which extend over several generations shows occasionally the first appearance of chondrodystrophy from normal ancestors, followed by orthodox dominant transmission till the present time.

In the birth of a chondrodystrophic dwarf from normal parents we witness the appearance of a changed gene, a mutation. As stable as genes are, reproducing their specific type unchanged thousands of times, once in a while they change and from then on faithfully reproduce themselves in their changed type. Careful studies, in Denmark, indicate that such a mutation from a normal to a chondrodystrophy-causing gene occurs once in 24,000 eggs or sperm cells, so that one out of 12,000 children from normal parents is a chondrodystrophic dwarf due to a gene which was not present in his parents at the time of their development. The causes of such mutations are not yet fully understood. Mutations are known for a variety of genes and are always numerically slight but yet possible causes for unexpected anomalies. New mutations thus are an additional source of genetically induced congenital anomalies.

This discussion of the genetics of anomalies cannot be more than a generalized review of some

basic principles. The words "usually" or "likely" have been interspersed intentionally. Even the genetics of those few traits which have been chosen as examples is, in some cases probably, in others certainly, more complex than indicated. A diagnostically single type of trait may be caused by different genes, a dominant in one pedigree, a recessive in another, linked in transmission with the sex chromosomes in some, not linked in other families. Even purely environmental agents may cause an effect which copies that of some well known gene. Such manifold ways of causation should not surprise us. The complex machinery of development is liable to many types of interference but the possibilities of response are limited.

Sometimes we can clarify the genetic aspects of an abnormality sufficiently to be helpful in the prognosis of its possible future appearance. At other times we have to admit a lack of insight. This must be a stimulus to further study. At present it may be surmised that the majority of congenital anomalies has a genetic basis. If this is accepted, the frequent but mistaken feelings of guilt of the parents concerned may be alleviated by explaining to them the shuffling of the genic cards which is still mostly beyond human control but which determines so much of our fates.

More important still, the recognition of variable penetrance of many unfavorable genotypes is cause for optimism in regard to possible future prevention of congenital anomalies. If, at present, 70% of the individuals whose genotypes makes them liable to have clubfoot do not develop the trait it seems not beyond hope to expect that someday we shall find the causes for this fortunate lack of penetrance. Once having discovered the causes we may then hope to find means of control so that penetrance of the anomalous genotype is reduced to zero. Thus, recognition of the genetic basis of anomalies does not lead to a fatalistic attitude but, on the contrary, to the search for specific, preventive agents.

General References

1. Gates, R. R., Human Genetics, New York, The Macmillan Company, 1946, vols. 1 and 2, 1518 pp.
2. Muller, H. J., Little, C. C., and Snyder, L. H., Genetics, Medicine and Man, Ithaca, N.Y., Cornell University Press, 1947, 158 pp.
3. Stern, C., Principles of Human Genetics, San Francisco, W. H. Freeman & Company, 1949, 617 pp.

MENTAL DEFICIENCY DUE TO PRENATALLY DETERMINED FACTORS

Herman Yannet, M.D.

Mental deficiency is closely related to the general problem of congenital maldevelopment. While accurate over-all data is not available, it may be estimated, on the basis of institutional statistics, that well over 80% of the cases of mental deficiency are the result of etiologic factors that are operative during the prenatal period.

It is now possible to classify, with reasonable accuracy, approximately 70% of all cases of mental deficiency into fairly well established clinical categories. It is the purpose of this paper to present a classification and to review briefly the various clinical syndromes and categories relating to prenatally determined cerebral maldevelopment.

The classification proposed is based on etiology, as well as the period during which the etiologic factor is operative, and is presented in Table I. The various causative factors may be divided into three groups: namely, those operative before birth, at birth and during the postnatal period. As previously indicated, the most important, not only numerically, but sociologically, is the prenatally determined group, and of these, the major number is contributed by the hereditary group. With one exception (hereditary idiocy), all of the conditions listed in this category have, in addition to the mental defect, certain clinical characteristics which make them recognizable, even though the available family history is noncontributory, and the patient is the only involved member of the family. Unfortunately, it is not possible to classify, on clinical grounds alone, many cases which, if larger sibships were present, might prove to be genetically determined. These will be found in the heterogeneous grouping listed as "undifferentiated." The actual number of cases of this type is unknown, but probably is of considerable magnitude.

TABLE I

ETIOLOGIC CLASSIFICATION OF MENTAL DEFECTIVES

I. Prenatal
  A. Genetic
    1. Familial
    2. Phenylpyruvic oligophrenia
    3. Congenital ectodermosis (tuberous sclerosis, neurofibromatosis, cerebral angiomatosis)
    4. Hereditary idiocy
    5. Cerebral degenerations (cerebro-retinal, cerebral sclerosis, gargoylism, etc.)
    6. Muscular dystrophy
  B. Infection (syphilis, toxoplasma, rubella)
  C. Irradiation
  D. Iso-immunization (Rh, ABO)
  E. Questionable or Unknown cause
    1. Mongolism
    2. Congenital cerebral palsy
    3. Cretinism
    4. Cranial anomalies (microcephaly, congenital hydrocephaly, craniostenosis, hypertelorism)
    5. Undifferentiated
II. Birth Trauma (anoxia, hemorrhage, thromboses, veno-stasis, etc.)
III. Postnatal
    1. CNS infections
    2. Cerebral trauma
    3. Cerebral vascular disorders
    4. Recurrent convulsions (?)
    5. Miscellaneous (asphyxia, poisoning, tumors, etc.)

A. GENETIC

1. The familial defective represents the largest classifiable group in the over-all problem of mental deficiency. While exact data are not available, it probably represents over 30% of all mental defectives. The diagnosis is based on the presence of a similar type of intellectual retardation in one or both parents, as well as in most of the siblings. While occasionally a sibling may have average intelligence, this is unusual, and one with superior intelligence is never seen in these families. Practically all familial defectives are in the moron category. Recently Benda[1] has demonstrated an increased incidence of various gross anomalies in the central nervous system of these children, especially in the spinal cord. In as yet unpublished recent studies, an unusually high incidence of moderately abnormal electroencephalograms were observed in this group as compared to the normal population (Deutsch, Robertson and Yannet). The occurrence of convulsive disorders in this group

TABLE II

INHERITANCE OF FAMILIAL TYPE OF MENTAL DEFICIENCY (HALPERIN[2])

	No. of Children	Distribution of mental status of siblings		
		Defective	Inferior	Average
Defective×Defective	111	57%	39%	4%
Defective×Inferior	81	35%	55%	10%
Inferior×Inferior	274	15%	57%	28%
Inferior×Average	93	3%	33%	64%

is somewhat larger than would be normally expected. The method of genetic transmission is extremely complicated and is probably dependent on multiple dominant genes. Table II on page 329 throws some light on this. The data were taken from a paper of Halperin.[2] It will be noted that when both parents are defective only 4% of the children are of average intelligence, the remainder being either of defective or inferior intelligence. When one parent is defective and the other inferior, the incidence of average intelligence rises to 10%. When both parents are inferior, 15% of the children are defective while only 28% are of average intelligence. When an inferior and average couple mate, only rarely is the child defective, although 33% will be inferior and 64% of average intelligence. This type of inheritance pattern throws some light on the futility of attempting to significantly reduce familial mental deficiency by the sterilization of the mental defective. Because of their large numbers as compared to the defective, the individuals of inferior intelligence are by far the major storehouse of the responsible genetic factors in this condition.

2. Phenylpyruvic oligophrenia, on the other hand, represents an entirely different type of hereditary mental deficiency. This condition was first described by Folling in 1934 and subsequently studied along biochemical and genetic lines by Jervis.[3-5] Clinically, a severe degree of mental defect is found in over 80% of the cases. Only rarely is a patient with this disease in the moron category while one with this metabolic abnormality and an average intelligence has yet to be described. The majority are poorly pigmented, being, as a rule, blonde and blue-eyed. No specific neurologic abnormalities are observed. The metabolic defect resides in the failure to metabolize phenylalanine resulting in high levels for this amino acid in the blood. Renal deaminization yields phenylpyruvic acid which is eliminated in large quantities in the urine. The amount appearing in the urine is primarily dependent on the intake of phenylalanine. On special diets in which this amino acid is present in only very small quantities, it is possible to reduce the amount of phenylpyruvic acid to the barest trace. When this is done, however, no noticeable change in mental status occurs. Actually, the relationship of the cerebral abnormality to the metabolic defect has not as yet been clarified. The diagnosis is made by the demonstration of phenylpyruvic acid which produces a deep green color when a few drops of 10% ferric chloride solution are added to a few cc. of previously acidified urine. The test should be routine on all severely retarded children in whom the mental defect is not adequately explained. Genetically, the condition behaves as a simple Mendelian recessive. The heterozygous state, unfortunately, cannot be recognized at present. The incidence of the disease is such that it has been estimated that approximately 1 to 2% of the population carry this abnormal gene.

3. The term "congenital ectodermosis" has been used to describe 3 conditions which show considerable interrelationships. These are tuberous sclerosis, neurofibromatosis and cerebral angiomatosis. Genetically, the conditions have been considered as Mendelian dominants, with a striking variability in expression. As a result the clinical pictures in each may be extremely variable, to the extent that the diagnosis may prove exceedingly difficult. Among mental defectives, tuberous sclerosis is by far the most common of the 3. The fully developed syndrome, which is much less common than the partially expressed clinical picture, consists of sebaceous adenomata, cutaneous angiofibromata, shagreen skin, retinal lesions, extracerebral neoplasia, severe mental deficiency and convulsive phenomena. In infants, the most common manifestations are the mental defect, cutaneous angiofibromata especially around the cheeks, and retinal tumors having a peculiar mulberry appearance. Even these appear at variable times and not infrequently the only manifestation for many years is the severe mental defect. However, other signs, sooner or later, make their appearance. The mental defect, when it is to be part of the final picture, is, as far as I am aware, always present from birth, and its degree remains fairly stationary. The sebaceous adenoma do not as a rule appear much before the 7th year and usually later. At about the same time, areas of calcification in the cortex, and especially around the ventricles may be noted in the skull roentgenograms. It is occasionally possible, in young children, before intracranial calcification appears, to demonstrate the cerebral tuberosities projecting into the lateral ventricles by means of pneumoencephalograms. In only the fully expressed syndrome (or one that will eventually be so) is the presence of severe mental deficiency invariable. It need not be present in the partially expressed state and, in fact, is more often not present under these conditions.

Neurofibromatosis is so closely related to tuberous sclerosis that one may raise the question as to a possible unitary genetic cause. Practically all the manifestations in one may be seen in typical cases of the other. In very young children a true differentiation may not be possible. Mental deficiency is rarely present except where the abnormality is extensive. The neurofibromata may involve any

nerve and vary in size from the smallest pea-size barely perceptible cutaneous growth to grotesque overgrowths in the extremities resulting in symptomatic elephantiasis. The question has been raised at various times as to whether the marked variability in clinical pictures in both tuberous sclerosis and neurofibromatosis may not be related to the problem of homozygosity and heterozygosity involving a dominant gene.

Cerebral angiomatosis is less closely related clinically to either of the preceding two conditions although bearing a certain superficial resemblance. It is characterized by usually extensive cutaneous hemangiomata of the face and forehead associated with angiomatous neoplasia of the cerebral cortex. The latter is suggested by the characteristic serpentine calcification seen in the skull Rngm. The calcification in these children tends to appear earlier in life than is true of tuberous sclerosis. Practically all cases, sooner or later, develop convulsive phenomena.

4. Hereditary idiocy, as its name implies, is a genetically determined severe grade of mental defect, which is transmitted as a recessive trait. It has no characteristic clinical picture except for the marked deficiency and actually cannot be diagnosed except by the presence of a similar condition in another sibling unexplained by any other cause. Its importance rests on the fact that it cannot be ruled out as a diagnosis in the case of a severely retarded child born to normal parents, and must be considered when advising as to future pregnancies. Fortunately, it is relatively rare in my experience.

5. The so-called heredo-degenerative cerebral diseases include a large number of poorly defined conditions, many of which at the present time can only be identified pathologically. A few, however, have recognizable clinical pictures which allow for exact diagnosis. In general they may be divided into two large groups: (1) those in which the degenerative process is confined essentially to the ganglion cells and (2) those in which the white matter bears the brunt of the degenerative condition. During infancy, CNS symptomatology alone does not allow for the differentiation between these two groupings. The presence of certain characteristic associated retinal changes in two varieties of the first group are pathognomonic of specific syndromes. In cerebro-macular degenerative disease (infantile Tay-Sachs disease, amaurotic family idiocy) the presence of the cherry-red spot in the macular region is diagnostic. In cerebro-retinal degenerative disease (juvenile Tay-Sachs disease) the retinal changes consist of a pigmentary degenerative process starting in the region of the macula but rapidly extending peripherally to involve most of the retina. In this condition there is no cherry-red spot and optic atrophy is almost invariably seen. Although both conditions have been designated as Tay-Sachs disease, and there are certain striking similarities in the appearance of the ganglion cells at autopsy, the clinical picture, course and racial distribution of cases make it likely that the genetic factors involved are not similar, and that the two conditions represent distinct entities. Infantile Tay-Sachs disease invariably begins to manifest itself towards the middle of the first year of life. While the juvenile type may have its onset at the same time, it frequently first shows symptoms after the 2nd or 3rd year. Its course tends to be slow, with visual and auditory impairment associated with a wide variety of neurologic manifestations, such as ataxia and other motor defects. Eventually mental deterioration of a severe degree is reached. It is compatible with a relatively long life, while the infantile type rarely extends beyond the 3rd year. Genetically both varieties of Tay-Sachs disease behave as simple Mendelian recessives.

Gargoylism should also be included in these ganglion-cell degenerative conditions on the basis of the cerebral pathologic picture. It may be recognized early in life, although not necessarily in its complete form. It is characterized by mental defec as a rule, corneal opacities, enlargement of the liver and spleen, abnormalities in the shape of the skull and face, and generalized chondrodystrophy. Recent reports by Reilly have suggested that, unlike the Tay-Sachs diseases in which abnormal lipoidal infiltrations are found in the ganglion cells, the material present in the brains and other tissues in gargoylism may be a complex carbohydrate, glycogen-like substance. The disease seems to behave as a Mendelian recessive trait.

Other types of ganglion-cell degenerative diseases have been reported, usually as isolated cases. Neither the clinical pictures nor the pathologic findings have been uniform to the extent that would allow for classification as those described above.

Under the general term of "cerebral sclerosis" are included a number of cerebral degenerative conditions in which the white matter is primarily involved. Clinically, developmental delay, abnormalities in motor tone and convulsions may start during very early infancy or during childhood. The course may be rapid, with death within the first year, or extremely slow and prolonged.

It is frequently impossible to differentiate these conditions from certain of the cerebral developmental anomalies except through pathologic studies. While specific identifying terms have been applied to some of these conditions (Pelizaeus-Merzbacher, Scholtz, Krabbe, Schilder), the clinical pictures are rarely if ever characteristic enough for definite diagnosis, without pathologic substantiation. Because of the difficulties in diagnosis, genetic investigations have been few and not too reliable.

6. Muscular dystrophy has been included only because the incidence of mental deficiency among these cases, while low, is still greater than can be accounted for on the basis of chance. Cerebral pathologic findings in cases of muscular dystrophy are not recorded and the explanation for the mental defect is not apparent. Genetically, most of the cases behave as Mendelian recessives.

B. Infections

These will be discussed in detail elsewhere, but should be mentioned in passing. At the present time we can recognize with reasonable accuracy three distinct prenatal infections which result in significant cerebral maldevelopment, namely, syphilis, rubella and toxoplasmosis. It is not unlikely that the future will implicate other infectious etiologies that are operative prenatally.

C. Irradiation

Although extremely uncommon, it is well established that fetal irradiation, especially during the early months of gestation, may seriously affect normal development. Clinically, the most common manifestation is microcephaly with severe mental defect. Other types of anomalies are possible, however. Murphy,[6] in a survey among gynecologists and radiologists, found that of 76 full term children irradiated in utero, 25 showed evidence of defective development and of these 17 had mental defect with microcephaly. Considerable experimental work on mammals has also shown a wide variety of cranial, eye and skeletal anomalies that may result from fetal irradiation.[7] The implications from a preventive point of view are self-evident.

D. Iso-Immunization

Maternal Rh iso-immunization may interfere with normal fetal cerebral development and result in extensive abnormalities of the CNS. Certain of the clinical manifestations are strikingly uniform and allow for accurate diagnosis. The most common clinical picture includes the following features: (1) severe mental deficiency, (2) asymmetric hypertonicity and weakness of the extremities, neck and back, and (3) choreo-athetosis. In practically all cases it should be possible to obtain a neonatal history compatible with erythroblastosis fetalis, and an Rh setup in mother and child consistent with this diagnosis. Frequently, anti-Rh antibodies may persist in the mother's blood even many years after the pregnancy in question. A less common clinical picture is characterized by mental deficiency associated with generalized hypotonicity and incoordination. Finally, clinical observations and statistical considerations make it likely that varying degrees of mental deficiency unassociated with readily apparent neurologic abnormalities may also result from maternal Rh iso-immunization. Recent studies[8] on ABO mother-child incompatibility with particular relation to secretor status (this refers to the presence of A or B factors in the body fluids of certain individuals) suggests the possibility that certain cases of congenital mental deficiency may be the result of maternal AB iso-immunization. The infrequency of a significant history of erythroblastosis fetalis in these cases, the normal incidence of first-born and complete absence of specific neurologic disorder suggests that the pathogenesis in these cases may be different from that present in Rh iso-immunization.

E. Conditions of Questionable or Unknown Cause

In this group are found a variety of conditions in which the clinical pictures are characteristic enough to allow for classification, although the etiology, aside from its congenital nature, is not definitely known or uniform in all cases.

1. Mongolism was one of the earliest conditions among the mentally defective to be classified. Certain of the associated anomalies found in a large proportion of these children (i.e., congenital heart disease, deformities of ears and extremities, defects of eyes, etc.) made it very likely that the etiologic factor was operative before the 2nd month of fetal life. Most of the clinical features which characterize the condition are the result of a basic defect in skeletal growth, particularly the long bones and skull. The present varying conceptions as to etiology may be grouped into two categories: (1) that the condition is due to environmental factors (i.e., intra-uterine) and primarily hormonal in nature; (2) that the basic defect is in the germ plasm (i.e., genetic factor). In favor

of the first possibility are the following two observations: a. the advanced average age of mothers of mongolian children, suggesting possible endocrinal imbalances associated with approaching menopause; and b. the increased incidence of pregnancy abnormalities such as bleeding, miscarriages in preceding or succeeding pregnancies, history of premature births, or variable periods of sterility, in the histories of mothers of mongolian children.[9] In favor of the second possibility (genetic) is primarily the evidence accumulated with respect to twins. With rare exceptions, when only one of twins is involved the twins are dizygotic; when both twins are involved, they almost invariably prove to be monozygotic.[10] While a final decision cannot be made at the present time, my personal feeling is in favor of a genetic factor. However, if this be so, its behavior cannot be described in the usual Mendelian manner, but must await further knowledge of, at present, unknown mechanisms that influence its expression, such as maternal age. As regards treatment, recent publications notwithstanding, there is no good evidence that the normal course of the condition can in any way be beneficially influenced by any available medicinal therapy, endocrine or otherwise.

2. The congenital cerebral palsies include those cases with motor defects resulting from abnormalities of the CNS excluding the spinal cord, and due to unknown factors that are operative prenatally. The type of motor defects are of two kinds, those associated with hypertonicity and those with hypotonicity. Incoordination is usually present in both types as may be abnormal uncontrollable movements (choreo-athetosis, dystonia, torsion spasms, etc.). The incidence of mental defect among the congenital cerebral palsies is not known. Among all cases of cerebral palsy, including also those due to factors operative at birth or during infancy, it is estimated that approximately 75% are of normal intelligence. I believe, on the basis of comparative data, that the incidence of mental defect is probably higher among the congenital cerebral palsy group than among the natally and postnatally acquired variety, however.

The possible nature of the factors responsible for congenital cerebral palsy aside from those already discussed, such as prenatal infections, iso-immunization, congenital ectodermosis and cerebral degenerative diseases, is difficult to discuss in our present state of knowledge. However, the importance of hereditary factors should not be overlooked. In a recent report[11] on cerebral palsy among those severely retarded mentally, at least 10% of the congenital group were genetically determined. This represents a minimum value since in many families the patient represented the only pregnancy, and in many cases it may be expected that future pregnancies were discouraged because of the problem of caring for the involved child. It is of interest that all of the cases considered hereditary in the above report were found in the symmetrically involved group, and especially in the hypotonic variety.

3. Cretinism probably represents the only endocrine disorder that seems to be specifically related to mental deficiency. While many children with mental defects may have endocrine disorders, in these cases the endocrine disturbance is essentially an associated condition resulting from the same causative factors responsible for the mental defect. Treatment directed towards the endocrine disorder in these cases has little or no effect on the mental status. Cretinism manifests itself in two clinical categories. Although in both types, the characteristic picture can be recognized within the first few months of life, in one type adequate treatment with thyroid gland substance will allow for practically normal development in all spheres, whereas in the other this is not the case. Treatment will result in practically normal physical growth but mentally the defect will persist with little or only moderate improvement. Whether these two varieties represent the same basic condition but of different degrees of severity, or whether they are the results of different causative factors, is at present unknown. Most cases of cretinism in this country are sporadic. Occasionally, patients are seen in whom the family history suggests a genetic basis.

4. The cranial anomalies include a heterogeneous group of clinical syndromes that are considered together only because the presenting sign in each is an abnormality in the configuration of the skull. While genetic factors undoubtedly play a role in some, a wide variety of causative agents are probably involved. It must be stressed that with few exceptions, the cranial defect represents only one aspect of the maldevelopment. In many cases, such as microcephaly, the cranial anomaly is secondary to the failure of cerebral development. In others, such as some of the craniostenoses and in hypertelorism, the noxious agent must be presumed to act not only on the skull but also directly on the cranial contents.

A. The term "microcephaly" has been used interchangeably both as a descriptive term, simply referring to a head size significantly smaller than normal, and as a specific category in the classi-

fication of mental defectives. This is unfortunate since it tends to group together a wide variety of conditions that have little relation to each other. As a category in our classification, microcephaly includes only those cases with a marked decrease in the size of the cranium but with relatively normal growth of the facial bones. The resulting picture is very characteristic, due to the extremely low cranial vault, which tends to make the lower face prominent. There are no motor defects, as a rule, and the mental retardation is in the imbecile or low moron category. There is considerable evidence of hereditary transmission of the recessive type in this condition, so that a proper diagnosis is important as regards parent counseling.

B. The craniostenoses include those conditions in which one or more of the cranial sutures prematurely fuse. The fusion may occur prenatally or at any time after birth. The resulting configuration will depend on the suture involved. The two most common varieties associated with mental defect are oxycephaly in which the coronal suture is involved, and scaphocephaly, involving the saggital suture. The inclusion of other sutures or parts of sutures in the fusion process explains the wide variety of configurations that have been described. In oxycephaly, the vault is high and appears to approach a rounded blunt top. The antero-posterior distance is greatly reduced as is the circumference of the head in many cases. In scaphocephaly the head appears long and narrow with a tendency for greater narrowing in the frontal region. In some of the cases with craniostenosis, definite pressure symptoms appear, including papilloedema, secondary optic atrophy and exophthalmos. As has been stated earlier, there is considerable evidence to indicate that the mental defect that occasionally is present is probably an associated rather than a resulting manifestation of the cranial defect. Other associated malformations indicating the occasional widespread nature of the defect include skeletal and joint anomalies, congenital heart disease, cleft palate, etc. The appearance of the mental defect as well as the other anomalies is uncommon except in the oxycephalic type. While the factor or factors responsible for the craniostenosis are generally considered to be genetic in nature, a uniform mechanism cannot as yet be completely accepted. Families have been described in which the defect behaves as an irregular Mendelian dominant and in others as a recessive.

C. Hypertelorism is an uncommon cranial anomaly that may be associated with variable degrees of mental defect, occasionally extremely marked. While the skull defect may include widespread abnormalities at the base, the clinical appearance is presumably dependent on an overgrowth of the small wings of the sphenoid bone resulting in a marked widening of the inter-orbital distance. There is no correlation between the degree of skull defect and the severity or even presence of the mental defect, since many of these children are of normal intelligence. It is of interest that congenital heart disease is found more frequently in this group than in any other classification.

D. Congenital hydrocephalus may be the result of a wide variety of etiologic factors acting prenatally. Moreover, the basic pathogenesis may be variable, since interference with adequate resorption of cerebrospinal fluid may follow defective development at many points in the spinal fluid pathways. As in other varieties of cranial anomalies, an associated mental defect may frequently be the result of the basic etiologic factor, rather than a manifestation of the hydrocephalus per se.

5. The term "undifferentiated" is used to denote all cases due to unknown factors acting prenatally and having no characteristics that would allow for classification in new or already established categories. It represents about 30% of all institutionalized defectives, and in the idiot category the proportion may reach as high as 75 or 80%. It undoubtedly includes a considerable number of genetically determined conditions which, however, cannot be recognized as such at the present time. The relatively large size of the undifferentiated group is an indication of the meagerness of our knowledge concerning the causes of developmental defects.

The relative numerical importance of the different varieties described above in the over-all country-wide problem of mental deficiency is not known. Such data are available only with reference to those defectives in institutions. Unfortunately, institutionalized mental defectives are a selected group; under no condition can they be considered as representative of the entire problem. This follows from the fact that admission to institutions caring for this type of child, whether private or state controlled, is dependent on many other factors aside from the mental deficiency. These include such considerations as home environment, familial economic status, availability of community care, presence of associated defects like convulsive disorders and personality-deviations, and many others. For example, it should be expected that the familial defective will account for a greater proportion of institutional beds, because of its peculiar genetic considerations. The parents being of defective or

inferior intelligence and the presence of other defective siblings would increase the need for institutional care, as compared to children with an acquired defect of similar degree of severity.

Table III summarizes briefly the incidence of various etiologic factors in 1729 mental defectives admitted during the last 10 years to the Southbury Training School, a state supported institution in

TABLE III

CLASSIFICATION OF 1729 INSTITUTIONALIZED MENTAL DEFECTIVES

I. Prenatal	
A. Hereditary (familial, phenylpyruvic, congenital ectodermoses, degeneration, etc.)	768 (45%)
B. Infection (syphilis, toxoplasma, rubella)	9
C. Iso-immunization (Rh)	12
D. Unknown or questionable (mongolism, congenital cerebral palsy, undiff., etc.)	789 (46%)
II. Birth Trauma	54 (3%)
III. Postnatal (CNS infection, trauma, etc.)	97 (6%)
Total	1729

rural Connecticut. It will be noted that approximately 45% are due to genetically determined conditions. The large proportion is in great part due to the great numbers of familial defectives as previously noted. An approximately equal number, about 46%, were due to factors operative before birth, but of unknown or questionable nature, such as mongolism, congenital cerebral palsy and undifferentiated types. Thus, almost 90% of all the admissions to the institution were due to developmental anomalies resulting from a wide variety of etiologic prenatal factors. Only about 10% were caused by natal and postnatal factors, there being twice as many of the latter group.

As might be expected, the prenatal factors responsible for the mental defect also interfere with normal development of extracerebral organs. This is particularly true of the heart and eyes, and to a lesser extent the extremities. Unfortunately adequate control data for comparative purposes are not available. The figures for the familial defective, representing the least involved, may be used for this purpose, although it must be remembered that even in this group, extracerebral congenital malformations are probably slightly higher than should be expected in a random population. Table IV

TABLE IV

MENTAL DEFICIENCY OF PRENATAL ORIGIN; INCIDENCE OF NONCEREBRAL MALFORMATIONS
(in per cent)

	Familial	Mongolian	Others
Heart	0.8	8.8	1.6
Eyes	0.3	7.6	3.1
Others	0.6	4.4	4.9

summarizes this material. The high incidence of congenital defects especially of the heart and eyes in mongolism, as well as in the other prenatally determined conditions is well demonstrated.

REFERENCES

1. Benda, C. E., Familial imbecile or oligo-encephaly as morbid entity, Am. J. Ment. Deficiency **49**:32, 1944.
2. Halperin, S. L., Human heredity and mental deficiency, Am. J. Ment. Deficiency **51**:153, 1946.
3. Jervis, G. A., Phenylpyruvic oligophrenia, Arch. Neurol. & Psychiat. **38**:944, 1937.
4. Jervis, G. A., Metabolic investigations on case of phenylpyruvic oligophrenia, J. Biol. Chem. **126**:305, 1938.

5. Jervis, G. A., Genetics of phenylpyruvic oligophrenia, Proc. Am. A. Ment. Deficiency **44**:13, 1949.
6. Murphy, D. P., Outcome of 625 pregnancies in women subjected to pelvic radium or roentgen irradiation, Am. J. Obst. & Gynec. **18**:179, 1929.
7. Warkany, J., and Schraffenberger, E., Congenital malformations induced in rats by roentgen rays: Skeletal changes in offspring following single irradiation of mother, Am. J. Roentgenol. **57**:455, 1947.
8. Yannet, H., and Lieberman, Rose, Mother-child ABO incompatibility, Am. J. Dis. Child. **76**: 176, 1948.
9. Benda, C. E., Mongolism and Cretinism, New York, Grune & Stratton, 1946.
10. Rosanoff, A. J., and Handy, L. M., Etiology of mongolism, with special reference to its occurrence in twins, Am. J. Dis. Child. **48**:764, 1934.
11. Yannet, H., Infantile cerebral palsy cases with severe mental deficiency, PEDIATRICS **3**:820, 1949.

CONGENITAL MALFORMATIONS INDUCED BY NUTRITIONAL DISTURBANCES OF THE EMBRYO

JOSEF WARKANY, M.D.

Dr. Josef Warkany, Cincinnati, was unable to participate in the Symposium because of illness. Dr. John A. Anderson, San Francisco, substituted for Dr. Warkany and presented in part work done by Dr. Warkany which has been previously published elsewhere. Dr. Anderson's presentation is not included in this publication of the Symposium. Readers are referred to Dr. Warkany's publications.

Pediatrics

VOLUME 5 FEBRUARY 1950 NUMBER 2

SPECIAL SECTIONS

THE PEDIATRICIAN AND THE PUBLIC

AN OPEN FORUM

PAUL A. HARPER, M.D., *Editor*

Statements appearing in this column do not necessarily reflect the opinion of the editor nor are they to be interpreted as the official opinion of the Academy.

INTRODUCTION

THIS issue contains two communications concerning the British National Health Service; a letter from Dr. Hugh C. Thompson, who is a member of the Tucson Clinic, Tucson, Arizona; and a reply by Dr. Edwards A. Park.

The first two papers are those which were presented by a panel of visiting experts who were invited to discuss the British National Health Service at the recent annual meeting of the American Public Health Association in New York City. The first paper is by Mr. J. T. Rice-Edwards, F.R.C.S., who appeared as the official representative of the British Medical Association. One point brought out in the panel discussion was that the present National Health Service in Great Britain is not the child of the Labor Government, but rather had been agreed to in principle by all major parties. As early as 1933 the British Medical Association had recommended to the government that the panel system which then covered less than 50% of the population should be greatly expanded. The Beveridge Report, which laid the foundation for the whole broad welfare program, including the National Health Service, was accepted in principle by Mr. Churchill's government in 1942. Mr. Rice-Edwards points out in his paper that the profession agreed to accept service under the Minister of Health and also to make the service available to 100% of the population in 1944, before the present government came into power. As Mr. Rice-Edwards says, the only thing then left for the profession was to secure the maximum amount of freedom within the service. It is probable that the details of the service would have been more agreeable to the profession if it had come into force under a Conservative rather than under a Labor government, but it was the consensus of the panel that the National Health Service would have come regardless of the complexion of the government.

The second paper, by J. S. Collings, M.B., is a most careful study of the general practitioner service which was undertaken by the author as a Nuffield Research Fellow. Dr. Collings made some explanatory comments concerning the methods used in this study which are not included in the present paper, but which indicated that the study was carefully done and is the best attempt to come to grips with the central problem which the editor of this column has seen. It is only fair to say that other papers given at this same session indicated the general satisfaction of the British public with the Health Service.

These two papers, together with that of Dr. R. S. Illingworth, published in the September issue of this column, constitute three different views on the British National Health Service. The comments of these writers upon the general practitioner's service are of importance to all thoughtful physicians. The barrier between the general practitioner and the urban hospital has been considerably greater in Britain than in this country. It now appears that the attempt to improve the quality of hospital service, particularly in the smaller hospitals, is still further limiting the scope of the general practitioner. The point is that the defects of the general practitioner's service are of long standing and that the additional load which has been thrown on doctors in general practice by the National Health Service is rapidly bringing the matter to a crisis. The problem involves all the relationships between the general practitioner and the specialist and is concerned with fundamental questions of medical education and practice which are of concern to physicians everywhere.

It is clear that improvement of the conditions under which general practitioners work and of the service which they provide is the most acute problem facing Britain's National Health Service. It may not be too much to say that success in solving this problem is essential to Britain's medical care program. Such a solution will be a long term matter and must cope with basic questions of medical education and practice as well as with the problems of services under the National Health Act.

Physicians in this and other countries will be watching this situation with great interest. The important long-time consideration is that the medical profession shall offer such service as to command public respect and shall provide such challenge and rewards to its members that it shall continue to attract to itself its full share of the top individuals from each generation.

* * *

Dr. Thompson's remarks are largely directed to Dr. Park and will not be commented upon here. However, in his final paragraph, Dr. Thompson says, "I would like to object strongly to a continuation of solicited articles on political matters if the column is to be run by physicians whose political philosophy is so far removed from that of the majority of the Academy. Information, both favorable and unfavorable, regarding medical care in foreign countries and in this country can easily be obtained from many sources today, and it seems unnecessary to have it in PEDIATRICS."

This concerns the current editor and calls for a brief statement on his part. He was himself engaged in and thoroughly enjoyed private practice in pediatrics for several years and is fully cognizant of the value of the doctor-patient relationship and the great importance of preserving it and other assets of our medical tradition. However, your editor believes that we are living in a period of change in many of our ways of life. Such change has and will continue to involve the practice of medicine and this cannot be avoided

merely by ignoring the forces which underlie it. The medical profession can no more afford to be ignorant of the factors which are influencing change in medical practice around the world than an employer can afford to disregard the forces which are changing his relations with his employees. It is the belief of your editor that the profession should be aware of changes in medical practice and that such information should be presented in reputable medical journals. Communications dealing with these matters should be sought from those best qualified to present them, preferably from individuals with medical training. It is correct that many communications to this column are not spontaneous; indeed it involves a considerable amount of work to provide material for the monthly issues. It is also true that the group which advocates change is more vocal than those who oppose change. For example, the editor of this column has for many months been trying to obtain a series of communications on group practice. There is no difficulty in finding those who favor group practice and who are willing to describe its advantages; but there has been a great unwillingness on the part of those who have had experience with the problems and growing pains of group practice organizations to describe their experiences, yet it would clearly be advantageous to have a recital of such facts if only to assure that future ventures in group practice might avoid some of the pitfalls of the past. The same situation holds on almost all controversial subjects.

The policy of your editor is to invite communications from individuals who take opposite views of a controversial subject. But a communication once invited must be published. If only one view is forthcoming then that alone is presented. However, those holding a contrary opinion always have the privilege of writing in and presenting their position as has been done by Dr. Thompson. One might inquire how long it has been in the democratic tradition to shut off opinion with which one does not agree, or again, how much thought would be stimulated by a communication with which all were in accord.

But the issue is not one to be resolved by conflict. The purpose of the column is to provide an open forum where various views may be presented and out of which may come some common meeting ground. In this connection it is pertinent to quote two paragraphs from a statement signed by the Maryland members of the American Academy of Pediatrics and presented in the August 1948 issue of this column on the subject of financial support of medical education:

"There is urgent need for a nation-wide, physician-sponsored program to improve medical care. The public demand for more medical care and for its better distribution cannot be satisfied by the statement that medical care is now adequate. It is to the credit of the profession that many local medical groups have acted to improve local medical service, but there is no professionally-sponsored, effective, country-wide program. The demand for such a program is not a local phenomenon; it is world-wide, and in many countries it has been strong enough to demand and receive action. Unfortunately, the physicians in many such countries have maintained a persistent, negative attitude toward this public demand with the result that laymen with more knowledge of political pressures than of medical needs have drafted legislative programs which have been imposed by popular vote.

"The public and their political representatives have been interested chiefly in the availability and in the cost of medical services. The overwhelming importance of quality and the need for protection of such intangibles as the patient-physician relationship which has been too often neglected in other countries should become the platform and the goal

of the profession in this country. It is our view that the adoption of a positive position by the physicians of this country for the improvement of medical care through better medical training will put the profession in a strategic position for future leadership."

It is incumbent on each of us as intelligent citizens and as physicians to approach this subject objectively, attempting to acquire as much information as possible to the end that each of us may in some way contribute to the solution of the problem. It is the view of your editor that this column should attempt to serve this same purpose and he will appreciate suggestions and assistance from members of the Academy which will help to achieve this end. Above all he will welcome spontaneous communications expressing individual views.

THE BRITISH NATIONAL HEALTH SERVICE: THE MEDICAL PROFESSION AND THE NATIONAL HEALTH SERVICE

By J. T. RICE-EDWARDS, F.R.C.S., *Hon. Asst. Secretary, British Medical Association, South Wales Branch*

In my capacity of Assistant Secretary to the South Wales Branch of the British Medical Association, and also in my practice as a surgeon, I am in very close contact with all branches of the profession. This gives me an excellent opportunity of hearing the general views of the practising doctors, more especially, perhaps, their complaints.

I think that it is true to say that the doctors generally did not want nationalised medicine and, whereas medical politicians had done a great deal of work on the subject, the average doctor was not really interested and never expected the health service to materialise. It was one of those things which came almost suddenly; they were naturally afraid of it, and still are, because, prior to July 5, 1948, it was a free profession, and any form of control was obviously unpopular.

The profession were lacking in enthusiasm and interest, and agreed with the then Minister of Health in 1944 to accept service under the Minister of Health, and also to make the service available to 100% of the population.

In the Monmouthshire Division of the B.M.A., of which I was then secretary, the 100% issue was agreed to, and it is interesting to recall some detail. I personally sent out 300 invitations to doctors, both members and nonmembers of the B.M.A., to attend a meeting where this question would be discussed. About 50 doctors attended, and the motion to make the service available to 100% of the population was carried, the voting being 17 for and 10 against. I know that most of the absent members were opposed to this issue, but they did not come to the meeting to say so. The fact remains that, owing to the apathy of the profession, such important issues were passed, almost unnoticed. It is only fair to add that the war was on, and most of us considered that we were doing more important work than attending meetings.

It will be seen from this, that having accepted service under the Minister of Health, and having accepted 100% of the population in the service, the only thing left was to secure the maximum amount of freedom within the service.

It must be realised that, prior to July 5, 1948, we were a free profession. General practitioners owned the goodwill of their practices which it was the custom to buy or sell, and perhaps it is convenient at this juncture to say a few words about the procedure of sale and purchase of practices. This is a subject I can discuss impersonally because I am

in consulting practice and therefore, in the ordinary way, would have no practice to buy or sell, although in the past, when I was in general practice, I have both bought and sold a practice.

It was an ordinary business transaction, with nothing sinister in the arrangement. What usually happened was that a young doctor wishing to start practice would, through a medical agency, be put in touch with a doctor who wanted a partner or wished to retire. A preliminary introductory period of three to six months would be arranged so that either party could withdraw from the transaction if the details were not satisfactory. The purchase price was usually in the region of 1½ years' purchase, and the money could be borrowed from the bank, or through the B.M.A., or through the agency.

I know of no more certain way of making a young doctor work hard, and what is more, want to work hard and look after his patients, than by owning the goodwill of his own practice.

Within the state service this is now illegal and, although many things in the act were left to regulation, the penalties for selling a practice are laid down in absolute detail.

So medical practice has passed from private to public ownership, and, in my opinion, the patient has lost a good guarantee of service and direct contact with his doctor. There is now a third party in the doctor-patient relationship, and the doctor is employed by the minister and not by the patient. Privacy is in jeopardy and the whole set-up tends to become less personal.

The policy of the Labour government was, originally, to introduce a full-time salaried service, but this has, so far, been successfully resisted by the profession. It was realised that this would have been incompatable with free choice of doctor, which could only be maintained by payment of the doctor on a capitation basis. For this reason the profession also successfully opposed the minister's original proposal for a universal basic salary of £300 per annum, as it would have been the thin end of the wedge for full-time salaried service.

The doctors have no objection to full-time salaried appointments for those who desire them, but that is quite different from forcing every medical practitioner into full-time salaried service, with no alternative.

Statistics show that 95% of the British public have entered the scheme, but it must be remembered that they are compelled to subscribe to it, whether they use it or not, and, if their names are entered on the list, they are entitled to free medicines, artificial teeth, spectacles, etc.

The minister has refused to give the same facilities to private patients.

Statistics also show that 19,000 out of 22,000 general practitioners have entered the service, but I think that you should consider the reasons for this. Any doctor who did not enter the service by July 4, 1948, would not be entitled to a proportion of the 66 million pounds which had been set aside as compensation for loss of the sale of the goodwill of his practice. So these figures cannot be taken as an indication of the popularity of the service.

The doctors, generally, are, at the moment, irritated and suspicious of the service, which is free and extravagantly used. The general practitioner is wasted on nonmedical matters, such as the excessive certification for benefits. Certificates are issued for glasses which are never worn, and drugs and medical accessories, often very costly, are wastefully used.

The question arises whether the novelty of this situation will eventually settle down, or whether the principle of everything for nothing will have to be modified, and some charge made for each item of service.

Consultations in the surgery and visits to the homes have increased enormously, often due to scares by government propaganda which created the belief that any little ache or pain was due to something serious, such as infantile paralysis or cancer.

It is not unusual for a doctor to spend 8 or 9 hours in his consulting room, mostly involved in trivialities.

General practice has become discredited to a marked extent, and it is noticeable that nearly all newly qualified doctors wish to specialize, and will not consider general practice.

As far as the specialists are concerned, they can be roughly divided into two groups, the whole-time salaried type and the visiting specialist who is also engaged in private practice. The visiting consultant is employed on a limited sessional basis, with a clause that three months' notice of dismissal can be given. There is, therefore, no security of tenure, and, as the ultimate aim is quite clearly shown to be a complete full-time salaried service, the process of elimination can be achieved by gradually reducing the part-time appointments. It must be remembered that all general hospitals have been taken over by the state, and, with the exception of the Catholic hospitals, all private hospitals and nursing homes can be compulsorily acquired in the same way. Thus the survival of the specialist, whose work consists of one or more part-time appointments combined with private practice, is in danger.

In the present hospital scheme, there is a tendency to general levelling down, which is discouraging to the more successful. Specialist status is more easily attained in some departments, due to an artificial system of grading, but opportunities of increasing a practice are becoming fewer and are governed by regulation.

The hospitals are overloaded with executive staff and the noble band of voluntary workers has been replaced by paid officials and their staffs. In the case of the smaller hospitals this appears to me to be unproductive and uneconomic and so far has not produced the extra beds which are so urgently needed to reduce the waiting-lists.

The hospital service is in danger of becoming a state monopoly, controlled by civil servants, and becoming stereotyped and impersonal, and with, eventually, no competition from private practice. One wonders how such undisciplined men as Lister or Jenner would survive in such a system.

It is considered that the set-up of the Act is too much in the hands of the minister and is too totalitarian. For instance, the governing body, the Central Health Services Council, consists of 41 members, 21 of whom are doctors, and, except for ex officio members, they are all appointed by the minister, and not elected by the profession. The Regional Hospital Boards, i.e., the governing bodies of the hospitals, are all appointed by the minister, and the hospital management committees are appointed by the regional boards. The profession consider that, at least, a few members should be democratically elected, as there is a tendency for political bias to influence these appointments.

I think that you will agree that medicine and politics are not natural companions.

I think that I have said enough to indicate the causes of much of the uneasiness which exists in the British medical profession.

I understand that a similar scheme is contemplated in your country, how similar I do not know. Whether you want it or not is entirely your own affair, but I would like to give you one piece of advice, and that is, to attend medical meetings and to see that 100% of the profession thoroughly understand your policy.

THE BRITISH NATIONAL HEALTH SERVICE: GENERAL PRACTITIONER SERVICES

By J. S. COLLINGS, B.Sc., Agr., M.B., B.S., *Research Fellow, Nuffield Provincial Hospital Trust*

There are many dramatic stories and reports in circulation about the frightful things that are happening to the time-honoured institution of general practice in Britain. Stories of how the general practitioner is being turned into a little cog in a vast bureaucratic machine; of how his previous high standards of work and service are threatened by the mechanisation of what was, before the fifth of July, 1948, assumed to be a highly individual and humanistic personal service; and of how the patient, previously so well cared for, has now become a mere number on a doctor's list to be dealt with and dismissed as quickly as possible. Some of these stories are half-truths, but the majority of them are the result of wishful and wilful thinking, and most of those which do have a basis in fact are symptoms of a long-term illness from which general practice suffers, and not an acute illness the cause of which is so readily assumed to be the new National Health Act.

The unfortunate general practitioner finds himself at the emotional vortex of many of the controversies which centre on the National Health Service. He has in fact become the victim of his own "glory," of last century concepts of "the family doctor," which have been carried forward to the present day, but which survive only in the world of fantasy, try as we will to give them reality. He is what Mannheim might call a "non-contemporaneous contemporaneity."

What exactly is general practice?

It isn't exactly anything. It is regarded as though it were an entity, a specific thing, which can be defined, observed and measured in standard and objective terms. However, it is not an entity, and defies comprehensive definition; it lacks standards and there are no established or accepted criteria for measuring or judging even particular examples of general practice. All this, together with the continued identification of general practice with an almost extinct ideal—"family doctoring"—is the basis of the long-term illness to which I have just referred.

In these circumstances, before we can consider what immediate and future effects the National Health Service Act is having or is likely to have on general practice, it is essential to try to understand the state of general practice at the time the Act was introduced.

As far as I have been able to ascertain, there were then three major types or "patterns" of general practice: (1) general practice in industrial areas; (2) general practice in "better class" urban residential areas; (3) general practice in rural areas. I want to tell you a little about each of these.

In terms of scope and quality of and facilities for medical care, "industrial" practice comes at the bottom of the scale.

The scope of work undertaken by the average general practitioner working in an industrial area was as limited as the volume was great. It was limited almost entirely to

Presented to Dental Health, Medical Care and Public Health Nursing Sections, Annual Meeting, American Public Health Association, Oct. 27, 1949.

Published here concurrently with its appearance in the February 1950 issue of the American Journal of Public Health, by agreement with the editor of the latter.

rapid diagnosis based on a minimum of consultation and examination and to such simple therapy as could be carried on with "bottle" and pill or syringe and needle.

The doctor's surgery or, as you would call it, his office, was most frequently a converted shop or residence—nearly always forbidding of aspect, functionally unsatisfactory and in absolute terms poorly equipped.

The doctor works within the limits imposed by his own surgery and equipment; he has had no access to the large hospitals and very little contact with his colleagues, either specialists or fellow general practitioners.

So limiting are these conditions that there is a levelling of "quality" of both individual doctors and standards of care. From the point of view of public safety the important consideration in such circumstances is the ability of the individual doctor to make a quick and correct diagnosis.

Hospitals (particularly outpatient departments) and Local Government Authority services compensate for the deficiencies of this type of practice; they do not supplement the routine work of the doctor.

The work of the G.P. has never been satisfactorily integrated with the work either of the hospitals or the Local Authority services, such as maternal and child welfare, midwifery, school medical, health visiting, etc.

At the upper end of the scale there is rural practice and here we find that the functions and responsibilities of the doctor still approximate rather closely to those of his prototype, the old "family doctor." The rural practitioner undertakes responsibility for a great many things; often for a certain amount of surgery which he does at the local cottage hospital, for the bulk of the diagnostic problems with which his patients present, for nearly all the obstetric work which is not grossly abnormal, for a certain amount of routine clinical pathology, and for the psychologic problems which assume an ever increasing importance.

His surgery or office is usually a pleasant establishment, functionally far from perfect but reasonably well equipped with the apparatus and instruments essential to his daily work. He knows his patients as people and his families as families. If he has the personal skills and the facilities provided by even a small cottage hospital and well equipped surgery, he can and does work on a high professional level. He is not as isolated as his industrial colleague; as a rule, specialists visit the cottage hospital from time to time and he at least has the benefit of intermittent contact with them.

When you are trying to visualise rural practice in England, it is important to remember that 30 or 40 miles is a great distance, that road, rail and telephone communications are good and that the real problems of geographic isolation, as you know them in America, simply don't exist.

Between these upper and lower limits we have what I have termed "better class" urban residential practice. Here the scope of the work undertaken by the doctor and the nature of the surgeries and equipment is something between the two extremes just discussed.

The best of these practices approximate to good rural practice, and the worst to "industrial" practice, but as a group they form a "type" of their own.

You will see, I hope, even from these brief remarks, that general practice is complex and that we must consider the impact of the National Health Service Act on its various manifestations and not on any hypothetic and undefined entity loosely termed "general practice." But before we go on to do this, I want to make some general observations:

1. General practice has adapted itself to the growth and development of hospital and specialist services; it has not developed concurrently.

2. The development of hospital and specialist services has most frequently been at the expense of general practice, not to its benefit.

3. This has been the case particularly where large hospital centres have grown up and has given rise to the paradoxic situation where, today, general practice is at its worst in closest proximity to the big hospitals and improves in both scope and quality in almost direct proportion to the distance away from the hospital centre.

4. This process of adaptation of general practice without concurrent development has gone on over a long period. Throughout this period general practice has enjoyed an immunity from analysis and criticism, and in its security it has failed to be self critical or to set and maintain standards.

Now let us examine the direct implications of the Act so far as it concerns general practice. There are three main points: 1. National Health Insurance has been extended to cover 100% of the population instead of the 40% covered before July 5, 1948. 2. New technics for remunerating the doctor have been introduced. 3. Provision has been made for the future development of Health Centres.

The extension of Health Insurance has thrown an additional load (both in absolute numbers and in demands for service) on the existing machinery of general practice; it has not altered its nature or structure. Just how great this additional load is, it is difficult to say. The latest Registrar Generals' Report puts it at 10% above a comparable period pre July 5, 1948. But whatever the size of the increase, the chief thing it demonstrates is the basic weaknesses in the present structure of general practice and the inability of the weaker parts to take the strain.

We may disagree with the principle of National Health Insurance, we may agree but think that this extension was untimely, but we are only fogging the issue if we try to attribute the shortcomings of general practice to National Health Insurance as such.

Much of the professional animosity to the new service stems from the doctors' real or imaginary interpretation of the intrinsic evils of receiving their financial reward in any other way than directly from the hands of their patients. I do not want to minimise the significance of this issue, significant if for no other reason than the emotional disturbances it has caused, but I must point out that once again technics for remunerating the doctor have nothing to do directly with the structure of general practice and to attempt to identify these two things, methods of remuneration and the structure of general practice, is again to cloud the issue. Furthermore, I would say that there is little concrete or observable evidence to support the popular contention that the doctors' conduct or way of practice is changing because of the introduction of the capitation system of payment.

Much of the noise and fuss over this issue is due to points petty in themselves, but personally annoying to the doctors and rightly classifiable as "teething pains."

The big issue, the hope and at the same time the despair of the general practitioner, is the question of Health Centre development. But before we go on to consider this, I want to say something about the indirect implications of the Act so far as general practice is concerned. These, despite the fact that they have caused little or no concern, are far more important than the direct issues, which have caused so much controversy and ill feeling.

I have pointed out previously how general practice has adapted itself to hospital development without itself developing concurrently and how other services, for example, those run by Local Government Authorities, have compensated for deficiencies in general practice instead of supplementing the work of this group of the medical profession.

The Health Services Act, by giving new impetus to hospital and specialist development and by altering and increasing Local Government Authorities' responsibilities in the field of medical care, has exacerbated this state of affairs.

This is leading to an intensification and worsening, so far as general practice is concerned, of the situation pre July 5, 1948, which has been briefly discussed.

General practice is now really under attack. It is an insidious attack, which is going on without anyone having the embarrassing task of openly criticising or naming the many serious shortcomings of general practice, as it is at present.

Strangely, the best elements of general practice are being attacked first and most strongly. The general practitioner-surgeon, who is normally the country doctor with cottage hospital facilities, is the No. 1 target. I would not want to defend the obvious and tangible mistakes of the G.P. surgeon, but I would point out that this man is usually, in general terms, the best of G.P.'s and that the vigour of the crusade against him is out of all proportion to the problem he presents and is being extended far beyond the defensible limits of surgery reform and into most of the other territory, which the G.P. can still claim as his own. It should also be noted that this "crusade" is being headed not by the lay "planners" but by the specialists, themselves doctors.

Hospital development as represented by the "upgrading" of small hospital units implies the elimination of G.P.'s from the staff and accordingly the "down grading" of general practice.

While this is going on, little or no attention is being paid to the weakest elements of general practice, which are found in the areas of dense urban population and which have been described previously. There is nothing left there which can be taken from the G.P. His many and important sins of medical omission (e.g., missed diagnosis) are not dramatic or tangible as are the sins of commission (e.g., surgical) of his colleagues in better circumstances, who still retain some measures of real responsibility, and so, for the time being, he is disregarded.

The trend is to reduce all general practice to the lowest common denominator.

In the face of the present state of general practice, Health Centres are the obvious and possibly the only solution to the problem. The Health Centre has been prescribed as the panacea for all the ills of general practice, but the conception of a health centre is quite as vague as the conception of general practice.

The positive steps which have been taken in this direction offer little to the G.P. in his present crisis. Authority for Health Centre development has been vested in Local Government and most of the thinking and planning for particular Health Centres has been oriented towards Local Authority services, with general practice again a secondary consideration.

Altogether the general practitioners are having less to do with the determination of their own destiny in the new service than anyone else. The Executive Councils, responsible for general practitioner services, and even the local medical committees, are completely preoccupied with the day-to-day problems of administration. They are not working or thinking in terms of policy, as, for example, are the Regional Hospital Boards. There is no co-ordination at the policy level between these two important bodies. This is not

just the result of a simple mechanical defect in the administrative set-up, which can be solved by appointing liaison officers or joint committees. Until policy decisions about general practice have been taken, there is nothing to co-ordinate.

In conclusion I want to say that I have deliberately tried to avoid discussing the many interesting and contentious issues, which provide most of the "copy" for those who write and talk about Britain's new medical service. Instead, I hope I have shown you a background against which these important "symptoms" can be given perspective and appreciated at their real worth.

Now to sum up:

1. General practice has long enjoyed an immunity from analysis and criticism. In its security it has failed to establish and maintain standards. In spite of this, due to the identification of all "general practice" with the ideal of "family doctoring," it has maintained the reputation of being good, per se.

2. At present, general practice is the weakest and at the same time the most important element in the whole medical service. The future of the service as a means of providing adequate medical care, as distinct from excellent and extravagant medical care at the hospital and specialist level, depends on the stabilisation of general practice. The financial future of the scheme may well also depend on this factor.

3. Such stabilisation, in turn, depends on a realistic assessment of the present condition of general practice and a clear definition as to the future province and function of the general practitioner.

4. In the absence of such an assessment and definition, present policy is resulting in the further deterioration of general practice.

5. The present issues of greatest contention, such as size of capitation fees, mileage rates, the number of patients on a doctor's list, the demand for spectacles, who should or should not get basic salaries or special inducement payments, etc., are all of them important to both the individual doctor and for their own sake, but unimportant so far as basic policy is concerned. The attention these matters are receiving is out of all proportion to their true significance.

So far as general practice is concerned the crux of the problem is how to convert it from a "non-contemporaneous contemporaneity" into something truly contemporary in both design and function.

DEAR DR. HARPER:

Dr. Park's article in your section of the November issue of PEDIATRICS has clarified many things concerning the conduct of this section of the journal. I feel that it warrants careful answering since I believe the section, as it has been conducted, has been doing a distinct disservice to the majority of the Academy members.

Dr. Park believes that his column has been an indication of a liberal and forward spirit not evidenced by any of the other organized groups of physicians. He also believes that his column has shown no bias, or at least that he has been unconscious of such bias. However, contributions to the column have admittedly been solicited, and it is evident that he has known both the writers of the contributions and their political philosophies beforehand. Articles describing forms of socialized medicine elsewhere have in general been neutral in their feeling and not unfavorable towards it. I am referring, for instance, to Dr. Illingworth's and Dr. Patterson's articles in the October number and Dr. Morgan's in the July number. It is true that Dr. Baehr was given a hearing, but there has been

very little expression of the opinions held by the majority of the medical profession in this country. I might also add that neutrality is not necessarily evidence of a liberal and forward spirit.

Dr. Park says that the chief reason why the physicians of the country are objecting to the proposal of compulsory health insurance is economic. Here I should point out that it has always been the system in America to allow great or reasonably great reward for fine achievement. An office boy can become Chairman of the Board and a haberdashery clerk can become President of the country. A practicing physician can achieve both the esteem of his fellow men and reasonable wealth. The successful physicians of this country are, in general, highly intelligent men with long years of specialized training, who work for more than the average number of hours, and who, in addition, have a personality and human qualities which appeal to their patients. This is a combination which would bring success and economic reward in nearly any business or profession. In return for the long hours of work necessary to achieve success in practice, especially pediatrics, with the consequent loss of spare time, contact with one's own children and family, etc., the physician hopes to secure not only the satisfaction of doing a job well, but also financial security, a good education for his children, and the means to enjoy whatever leisure time vacation and old age may bring him. To expect the physician to welcome, or not to oppose, a change which brings him the same long hours of work and even more, but without the remuneration that he now can achieve, would be very strange, especially as there is no evidence to show that the proposed substitute would bring better medical care for the patients. Most physicians today who have been in practice any time are working close to the limits of their capacity. The added burden of additional patients, plus the necessary filling of forms, can scarcely be visualised as improving the quality of care, or the amount which the average patient would get.

Dr. Park presumes that compulsory health insurance is inevitable, and that once we have it we will like it. He may be right in his opinion, but many people do not agree with him, and certainly most physicians hope he is wrong, and are contributing their money, and in many cases their time, to oppose this change.

Dr. Park then analyses possible methods of remuneration for doctors, as he seems to feel sure that a fee-for-service method of remuneration will soon vanish. The American public has not yet relinquished the fee-for-service principle in housing. They do not want to pay rent for a three-room house, whether or not they are living in a trailer or a mansion. Nor have they given up the fee-for-service method in regard to their food, their clothing, their insurance or their amusements. Dr. Park is considerably premature in assuming that they are willing to abandon entirely the fee-for-service system for medical care. He says it is the sheerest nonsense and bunk to maintain that the physician-patient relationship depends on an economic factor. As one who has had considerable experience in both clinic and private practice, I cannot agree that it is possible to maintain the patient-physician relationship to anywhere near the same extent in clinic practice, or army practice, or veterans' practice, as it is in the private practice of medicine. Most patients feel the same way, and accept the former methods of care only because they can get no other. Basically the doctor-patient relationship is a matter of the heart, but in no phase of our existence today is it possible to entirely disregard the economic factor, and many Americans still take pride in paying the doctor of their choice, and feel more trust in him, and more freedom in using him, because they pay him.

In discussing the situation in foreign countries, Dr. Park makes a rather amazing state-

ment that, "I know no reason to think that British physicians are less well educated than ours." Having had the chance to visit three British medical schools during the war, and to have close and intimate contact with British physicians for 15 months, and having talked recently to physicians who have returned from rather extensive visits in England, I feel that Dr. Park cannot be well acquainted with British medical education, as it has been, and is now. This is particularly true in the field of pediatrics, where the British physician has relatively little knowledge or training as we know it here in this country. In the entire city of Belfast, for instance, a city of approximately a half a million, with what is considered one of the best medical schools in the British Isles, Queen's University, there was only one full-time pediatrician, who, with the assistance of practitioners who did pediatrics part-time, was responsible for the entire education of the medical students in pediatrics, as well as for his own private practice.

Dr. Park expresses his philosophy regarding compulsory health insurance, and ends up by saying, "I am not opposed to compulsory health insurance if it comes to pass as an evolutionary development." Dr. Park certainly has every right to his own opinion, and it may even be that he is wiser than the rest of us in this matter. The fact remains, however, that the great majority of practicing physicians and pediatricians today are bitterly opposed to the idea of compulsory health insurance, and believe that it would be very wrong, both for the public and for their own profession. Inasmuch as "The Pediatrician and the Public," despite the fine print at the head of the column, represents the closest thing to an expression of political opinion which the Academy of Pediatrics has, and inasmuch as the members are judged by this column as to their political opinion by the rest of the medical profession and by the public at large, I would like to object strongly to a continuation of solicited articles on political matters if the column is to be run by physicians whose political philosophy is so far removed from that of the majority of the Academy. Information, both favorable and unfavorable, regarding medical care in foreign countries and in this country can easily be obtained from many sources today, and it seems unnecessary to have it in PEDIATRICS. The Academy of Pediatrics started off as a scientific organization, and as such has contributed much to the advancement of child care in this country. While its management has not been previously in any way a democratic one, few members, and I have been one for 13 years, have objected to this as long as the Academy confined itself to scientific matters. Now that it has entered into the field of medical politics I feel that the majority, who are practicing physicians, and not full-time teachers, should definitely control public expressions in this realm. I do not believe the majority wish either to be portrayed as neutral on compulsory health insurance, or to be educated to accept it. In fact, I believe that the majority would prefer to have PEDIATRICS become an outstanding scientific journal, and not allow it to be used as a sounding board for the political philosophies of individuals, no matter how scientifically eminent those individuals may be.

(Signed) HUGH C. THOMPSON, M.D.
Tucson, Arizona

DEAR DR. HARPER:

I should like to reply to Dr. Thompson's letter. I regard it as a clear, direct, self-contained expression of a kind which the editor of the Column most desires. I should probably leave Dr. Thompson's letter unanswered if I did not believe that he had started wrong impressions, concerning both what I actually said in my letter in the November

issue of PEDIATRICS and what I think. Dr. Thompson writes, "Dr. Park says that the chief reason why the physicians of the country are objecting to the proposal of compulsory health insurance is economic." With all due respect to Dr. Thompson, I did not say this. The idea which I tried to convey was that the economic factor is the crux of the entire medical care problem, that is, it is at the bottom of almost all difficulties in bringing to pass even small advances in medical care. I tried to point out further that this was justifiably so. I believe that if the economic factor could be eliminated in a manner completely satisfactory to the medical profession, the solution of the medical care problem would be easy. I quite agree with Dr. Thompson that other important factors in addition to the economic one are involved in almost all proposed changes in our medical care system. Ceilings on income and on the opportunities to rise in the profession such as now cover-in the general practitioner in England would be as intolerable to me as to him.

Dr. Thompson further states, "Dr. Park seems to feel sure that a fee-for-service method of remuneration will soon vanish." Again with due deference to Dr. Thompson, I never said any such thing. What I did say was merely that the "sliding scale" fee-for-service would be unworkable under any system of insurance for medical coverage, whether voluntary or not. My letter was perfectly clear on this point.

If Dr. Thompson will read my letter carefully, he will perceive that when I discussed the relative values of the fixed fee-for-service, the capitation and the salary methods of payment, I had reference solely to those methods possible under an insurance system, either voluntary or otherwise. If an insurance system had not been under discussion, the topic would never have come up at all.

Dr. Thompson states that contributions to the Column have been admittedly solicited. Some have been solicited, others not. He goes on to say that it is evident that "he" (I) "has known both the writers of the contributions and their political philosophies beforehand." In some instances I have known the writers, in others I have not known them. In some instances I have known their philosophies; in other instances I have had no idea what they were. Dr. Thompson gives three examples: Dr. Illingworth's and Dr. Patterson's articles in the October 1949 and Dr. Morgan's article in the July 1949 issues of PEDIATRICS. I should like to explain how I happened to select Dr. Illingworth and Dr. Patterson as authors of their respective articles. Under the belief that the great majority of the reports were biased on one side or the other, I was anxious to obtain for PEDIATRICS as fair an evaluation of the British Medical Care Program at the end of its first year as was possible. Dr. Donald Patterson, certainly one of the most outstanding English pediatricians and well known to a large number of Academy members, had recently moved to Vancouver, B.C., to take up pediatric practice there. It occurred to me that Dr. Patterson, then in a completely detached position in Canada, would be the one to give me the name of an English pediatrician who could write the truthful and fair appraisal which I desired. Meeting Dr. Patterson at the Academy meeting in Atlantic City a year ago, I asked his advice and he suggested at once the name of Dr. Illingworth. I had no idea whether Dr. Patterson approved or disapproved of the English medical care program. I had no idea whatsoever, when I invited Dr. Illingworth, whether his ideas were in favor of the present medical care system in England or were opposed to it, and I had never had the pleasure of meeting Dr. Illingworth. Having re-read Dr. Illingworth's article with great care in the light of Dr. Thompson's letter, I again gain the impression that Dr. Illingworth fairly leaned over backwards in an attempt to take an objective, impartial view. The English system was imposed without due preparation, more or less as a revolu-

tionary measure. It is obviously destined to undergo an extensive evolution as trial reveals its errors. Ten or 20 years from now its form will doubtless be far different from its present form. Its total success or failure as a medical care system for a nation cannot be judged until at least 10 or perhaps 20 years have passed. All a fair-minded critic could do at the end of its first year was to make its nature plain and attempt to point out its good and bad operational features as they had come to light during that time. Dr. Illingworth has attempted to do this.

In regard to Dr. Patterson's own article, may I say that I thought the experiment in medical care in British Columbia, according to which the local government established a system of insurance to cover the cost of hospital care so that it would be available to all citizens, but left medical practice undisturbed, was exceedingly interesting and should be reported in PEDIATRICS. I considered myself fortunate in prevailing on Dr. Patterson to make the report, since I knew that he would be accurate and impartial. Dr. Patterson's report is entirely factual. At no point does he indicate whether he favors the scheme or opposes it. I had no idea in approaching Dr. Patterson what his attitude toward the medical care plan in operation in British Columbia was, and do not know now. Dr. Patterson does remark that the plan has been advantageous financially to the practicing physicians there, including the pediatricians. If Dr. Thompson objects to Dr. Patterson's article, it must be on the ground that he is not interested in the experiment and does not care to know about it.

I was completely conversant with Dr. Morgan's article beforehand and know Dr. Morgan well as one of the most universally respected physicians in the country. Just as Dr. Black's article in PEDIATRICS (April, 1948) was interesting and important because it presented a very definite point of view, so I thought Dr. Morgan's address was important because it also offered a particular point of view. Dr. Morgan's thesis was, "I believe that the AMA should become the champion of the movement to improve and extend medical care in the United States and this because the American Medical Association . . . recognizes, indeed, insists that medical care in the United States should be improved and extended." I am completely at a loss to know why any member of the Academy, no matter what his philosophy, should fail to be attracted by what Dr. Morgan said, since he brought forward unusual points of view and the supporting statements were true and could not be gainsaid.

The question whether English physicians are equal professionally to American physicians is of trivial importance. Pediatrics has never been developed in England as a specialty. The pediatricians there have acted essentially as consultants. I know some of them personally and by their writings and believe them to stand with the best we have in this country. But they are few in number, and so far as the extent of pediatrics in England is concerned Dr. Thompson has admittedly scored a point. The question whether the necessity for the physician performing a medical service to send the patient a bill for that service is essential to the best physician-patient relationship is also of minor importance. Certainly the patient-physician relationship does not depend on any fee factor; the sole question is whether the fee factor enhances the relationship. It is difficult for me to think that it does. But Dr. Thompson has more experience in private practice than I had had and is in a better position to judge.

I believe that the issue between Dr. Thompson and me involves not so much "bias" as attitude when one is brought face to face with a complex problem such as the form which medical care in this country should take. In regard to the latter problem, I had

assumed as editor of the Column that the members of the Academy have been able to retain open minds and would wish, as I would wish, to have the benefit of not only all existing information in regard to experiences and experiments in medical care everywhere, but also of new ideas. I gain the feeling on re-reading Dr. Thompson's letter that the fault which he finds with me as the past editor of the Column is that I have attempted to give too wide an outlook to the readers of PEDIATRICS. Dr. Thompson must be careful in accusing me of bias not to do so on the ground that I have not conformed to a certain bias of his own.

As soon as my letter went off to PEDIATRICS, I realized that I had made statements which were susceptible of misinterpretation through mistaking detached thinking for wishful thinking. When I wrote, "I am not opposed to compulsory health insurance if it comes to pass as an evolutionary development," the medical care program in Sweden was in my mind. There, with the powerful support of organized medicine, voluntary health insurance became compulsory after a long period covering years. By evolutionary development of a medical care program, I meant a step by step advance through the process of trial and error as the result of collaborative efforts of the medical profession and the public. The implication is that the medical profession themselves would be partners in the development. If compulsory health insurance came to pass as an evolutionary development, as I define it, I should not be opposed to it. That is the idea which I intended to convey. In writing, "When organized medicine endorsed the principle of voluntary insurance as a means of meeting the general medical care problem, it placed itself on an incline on which it is destined to slide by degrees until it will be forced to accept and advocate compulsory health insurance," the opinion was based on an attempted cold consideration of the facts. If voluntary insurance is a correct principle for covering the cost of medical care of people with moderate incomes, it is bound to spread upwards to the people of higher incomes and it will of necessity spread downward to the people of lower incomes since these latter will demand to have it made available to them. When it has spread so that the great majority of people are covered by it, it is a small step for it to become compulsory—exactly what happened in Sweden. If it comes about in this way, it would be an extremely gradual evolutionary development.

I am as much opposed to the superimposition of compulsory health insurance as envisaged by the Truman Administration as is Dr. Thompson himself. However, I believe there is just one way in which the threat of compulsory health insurance can be effectively stopped, and that is for the American Medical Association to develop a comprehensive medical care program, so definite that it can be put side by side with any other program and so satisfying to the public and to the medical profession that rival plans will die a natural death. Every thoughtful person must realize that if a depression came tomorrow, in our present state of inaction, Congress would pass unwise medical care legislation even if it did not pass President Truman's National Health Program. It is my hope that the American Medical Association in their conferences with the American Public Health Association, the American Public Welfare Association and the American Hospital Association has at length started to develop such a program. At this important time the Academy could be of enormous help to the cause of child care if it could, in some formal way, bring to the attention of the American Medical Association the defects in medical education and child care as brought out in the Academy studies and ask the American Medical Association to consider them in its joint deliberations.

(Signed) EDWARDS A. PARK, M.D.
Baltimore

TRENDS

By JOHN P. HUBBARD, M.D., *Contributing Editor*

This and subsequent descriptions of events and trends are intended to be unbiased and factual, presenting both sides of controversial matters so that conclusions may be formed from critical appraisal of things as they are. These statements do not necessarily reflect the opinion of the writer nor are they to be interpreted as official opinion of the Academy.

STATE Chapters of the Academy continue to show evidences of action to meet the needs revealed by the Academy's Study. At an opening meeting of the Massachusetts Chapter, Dr. James M. Baty and Dr. Lendon P. Snedeker reviewed the findings to which first attention is being given and various steps already being taken. They reported as follows:

Dr. Baty: "The Massachusetts Study of Child Health Services has now completed its survey and published its findings. . . . We shall not review at this point the detailed findings of the Study, but limit our discussion to the principal facts which have been disclosed, and consider what action may profitably be taken on them.

"The Massachusetts Study was not undertaken until approval had been secured from the two most important professional bodies in the Commonwealth which were concerned with the outcome of our efforts: the Massachusetts Medical Society and the Massachusetts Dental Society. Early contact was also made with the Massachusetts Department of Public Health which from the start gave us their fullest cooperation and support. . . .

"Explaining the motives underlying the Academy Study was no easy task back in 1946. It was obvious that we needed to know more about the health service provided for children, and conversely something about their needs, but the motives of the Academy were suspected by some of our colleagues, who occasionally seemed to think that we were conjuring up the evil genie of State Medicine for playing "footie" with the Children's Bureau. The most baffling problem was explaining what we intended to do with the Study findings. Now that the job is completed, we feel that our vague aspirations were justified. There is work to be done."

Dr. Snedeker: "I shall not here enumerate the findings of the Study in detail. . . . Most of the rabbits drawn from the Academy hat are old friends, known to all of us who have lived with the health problems of childhood. Now their color can be described, their age has been computed and physical measurements have been taken. Discrimination is born of measurement and we can now defend our statements.

"The Study has quantitatively measured the existing health services for children and we now have a base of operations in working for their improvement. Furthermore, we can assign reasonable priorities to our efforts and decide geographically the areas where action is most needed. Although many of you may have looked over the report or read the condensed article in the *New England Journal of Medicine,* I think it would be well to review a few of the findings:

"1. There is need to improve the training, both undergraduate and graduate of medical men with regard to the care of children. This problem is basic but in many ways a problem to be tackled on a national basis. Your Committee for the Improvement of Child Health is now holding a series of conferences with medical educators to consider what

steps it is practical to take for improving the pediatric training of medical students. Locally, our pediatric societies can do a great deal for postgraduate education in cooperation with established medical groups.

"2. There is need to improve safeguards against infection in newborn nurseries and in hospital wards caring for children. The Academy should define standards for the hospital care of children.

"3. Many of our community health services for children need an overhauling. They are not evenly distributed. Personnel need more training and supervision. There is duplication of effort in some communities.

"4. Doctors and dentists, like health services, need better distribution.

"In the course of the Study inquiries have been received from certain of our members for information which we were quite unable to provide. The Study only covered certain points and the findings can only be stretched so far. We have produced various rates of health service, for example, but we cannot talk about those children not receiving any care.

"We have had opportunities to discuss the report with students at Harvard Medical School and the School of Public Health. Data have been furnished in connection with two doctorae theses. The Study material is on file at the Harvard School of Public Health and available to any interested and qualified individuals on application to the State Chairman of the Academy.

"We should very much appreciate critical comment on the Report from members of the Academy or the New England Pediatric Society.

"It does not seem to your Executive Committee that it is necessary or wise to determine the pattern of our future action solely by the Study findings. It happens that during the time the Study was undertaken a number of other reports were made in Massachusetts regarding current health practices. All of them should be included in our arsenal of fact and opinion. I refer to:

"1. The *Report of the Boston Finance Commission* on the Boston Health Department.

"2. *The Greater Boston Community Survey.* A considerable portion of our Study data were used in writing the health section of this report, which is concerned with available services for about half of the population of the Commonwealth.

"3. *House 2100—Report of the Special Commission to Study and Investigate Certain Public Health Matters.* This recess commission of the Massachusetts Legislature considered such basic problems as the development of local full-time health units. Its Technical Committee on Maternal and Child Health included in its membership four members of the American Academy of Pediatrics. This commission considered in the field of maternal and child health certain short-comings in the present management of school health, vital statistics, services for the handicapped, and the lack of adequate standards and remuneration for health personnel. Already, as a result, changes have been made in the law regarding the care of premature infants.

"Just what is practical to undertake in the light of these findings against a national background of growing tension and uncertainty in the field of health service? It is the feeling of your Executive Committee that the Academy of Pediatrics and its Committee for the Improvement of Child Health have been right in focusing the attention of the Academy membership on the very basic problem of medical education of our future medical practitioners, those who will be responsible for providing the bulk of medical service to children and whose training is inadequately weighted to suit them for their

responsibilities. Just how this better education is to be financed is a matter for debate.

"Massachusetts is not suffering from a lack of health service. Rates of care are high in comparison with many other states. However, the results are not optimal considering the amount of care rendered, and there is a maldistribution of service. It is not a question of more hospital beds, but how those beds are utilized and whom they serve. It is not so much a dearth of community services, but their distribution and content.

"It seems to your Executive Committee that one important first step in improving health services for children would be to increase the conscious participation of pediatricians and all those physicians interested in the children in the current activities of already existing medical organizations and in local community and hospital activities relating to children.

"By vote of the Executive Committee of the Massachusetts Study certain action has already been taken along this line. In 1946 the Council of the Massachusetts Medical Society referred the matter of the Study of Child Health Services to its Committee on Public Relations. On his own initiative the Executive Secretary met with the members of this committee and explained our aims and actions. However, health service is only indirectly a matter of public relations. It is more definitely a matter of public health. Therefore the State Chairman, Dr. Baty, requested the Council of the Massachusetts Medical Society to refer the Study to its Committee on Public Health. This Committee met on November 21 and has requested suggestions from the Academy members in the Commonwealth with regard to the creation of a subcommittee to consider the Study and its implications. Furthermore, Dr. McKittrick, the President of the Massachusetts Medical Society, has asked for suggestions with regard to more adequate pediatric representation on various committees of the Society whose activities should be a fundamental concern of pediatricians. It is significant that of nine committees of the Massachusetts Medical Society intimately concerned with the welfare of children, only two have pediatric representatives. Remember that children constitute about one third of the population and that one third of the practice of the general practitioner is concerned with children under the age of 15. These committees are:

1. Committee on Public Relations
2. Committee on Legislation
3. Committee on Medical Education
4. Committee on Public Health
5. Committee to meet with the Massachusetts Hospital Association
6. Committee on Postgraduate Medical Education
7. Committee on Medical Economics
8. Committee on the Postgraduate Assembly
9. Committee on School Health

"This situation may indicate a certain lack of interest on the part of pediatricians in the business of organized medicine. More likely it is evidence of lack of appreciation on the part of the profession as a whole that a relatively large proportion of medical practice is necessarily concerned with children. Apparently everyone has been content to let us go off in our corner and transact our own business. Under present circumstances such isolation is unproductive and imprudent. We must all work together for the solution of our present medical problems. It would be unfortunate indeed if the pediatricians of Massachusetts did not work cooperatively with the rest of the profession in the Commonwealth. They have in their possession a unique body of information which concerns one third of all practice and one third of the population of Massachusetts."

Dr. Baty: "Your Executive Committee has been charged with drawing up an inclusive program for the improvement of child health in Massachusetts. We feel that it is unnecessary and unwieldy to develop a set of committees outside the framework of the Massachusetts Medical Society. In terms of numbers, the profession as a whole is much more involved with children than we can ever be. We shall, of course, form such committees as are required for the conduct of Academy business and for the development of our national program. Your Committee, therefore, submits the following recommendations for your consideration and approval:

"1. We recommend that the Massachusetts Chapter of the American Academy of Pediatrics request the Massachusetts Medical Society to form a Committee on Child Health. It is suggested that this Committee include in its membership members of the Committee on Public Health, the Massachusetts Chapter of the American Academy of Pediatrics, the New England Pediatric Society, and the Massachusetts Department of Public Health and that it should include in its membership or call in conference members of all organizations in the Commonwealth concerned with the promotion of child health.

"We recommend that this Committee on Child Health undertake in cooperation with the Massachusetts Chapter of the American Academy of Pediatrics a program for the improvement of child health with the following suggested immediate and long-term objectives:

"Immediate Objectives:

"A. The development of pediatric representation on all committees of the Massachusetts Medical Society concerned with education, hospitalization, legislation and public health.

"B. The development of suitable standards for the hospital care of children and newborn infants. The recently published work of the Committee on the Fetus and Newborn of the American Academy of Pediatrics is an example in point.

"C. The appointment of a pediatrician as soon as is practicable to the Board of Registration in Medicine.

"Long-term Objectives:

"A. The conduct of infant mortality studies in collaboration with the Committee on Maternal Health of the Massachusetts Medical Society.

"B. The study of existing community health services for children and the development of measures for their improvement.

"C. The development of a program for continuing certain phases of the Study, in order that progress may be measured and action continue to be based on up-to-date information.

"D. The promulgation and support of effective legislation for the improvement of child health, including local full-time health services.

"E. Liaison with other groups concerned with the welfare of children, especially in the field of education.

"F. The study and improvement of the present distribution of medical services for children.

"2. We recommend that in the near future the Massachusetts Chapter of the American Academy of Pediatrics hold an open meeting for the purpose of discussing the findings of the Study and their implications for all child health organizations in the Commonwealth."

PUBLIC HEALTH, NURSING AND MEDICAL SOCIAL WORK

MYRON E. WEGMAN, M.D., *Contributing Editor*

AVERAGE INCIDENCE AND EPIDEMIC RECURRENCE OF POLIOMYELITIS

GEOGRAPHIC variation in the incidence of poliomyelitis is not well understood and many of the factors involved have not been properly evaluated. A large scale study of two important phases of this problem has recently been reported by Alexander G. Gilliam, Fay M. Hemphill and Jean H. Gerende (Pub. Health Rep. 64:1575 and 1584, 1949). These investigators studied the reported incidence of poliomyelitis in all the 3,095 counties in the United States and analyzed the data chiefly from the standpoint of variations in average annual incidence and the frequency with which epidemics recurred in a given locality.

The problem is complicated, as in many other diseases, by lack of a generally available specific diagnostic test. There is usually little question about the manifest cases with paralysis. Abortive and nonparalytic cases, however, constitute a large variable. In any large scale epidemiologic study one is forced to rely on reports of cases as received by the health authority. While there is provision for correcting these reports if subsequent events cause a change in diagnosis it is obvious that in any locality interest and awareness will largely determine the number of cases reported when there is no paralysis.

"It appears necessary to emphasize that in most States in this country no distinction is made between paralytic and nonparalytic poliomyelitis in cases officially reported. Although personal experience (Gilliam) suggests that the true ratio of paralytic to nonparalytic disease varies with epidemics, the situation is not infrequently encountered where suspected abortive and nonparalytic disease is reported officially in one county and only paralytic disease registered in an adjoining political jurisdiction patently involved in the same epidemic. In addition, though poliomyelitis is probably better recorded in this country than many other communicable diseases, completeness of reporting varies considerably from time to time and from place to place. It must be emphasized, therefore, that this study deals with poliomyelitis reported in the counties of the United States for a 15-year period, 1932-46."

The results of the study in regard to average annual incidence are shown in the map (see Chart 1).

"When this map is divided into northern and southern sections by the parallel representing a general westerly continuation of the southern border of Virginia, it is observed that:

"1. Of the small proportion (2.68%) of counties reporting the highest rates, most lie in the northern section with little other tendency towards geographic concentration evident.

"2. No tendency towards grouping nor sectional predilection is manifest by the counties (2.65%) in which no cases were recorded.

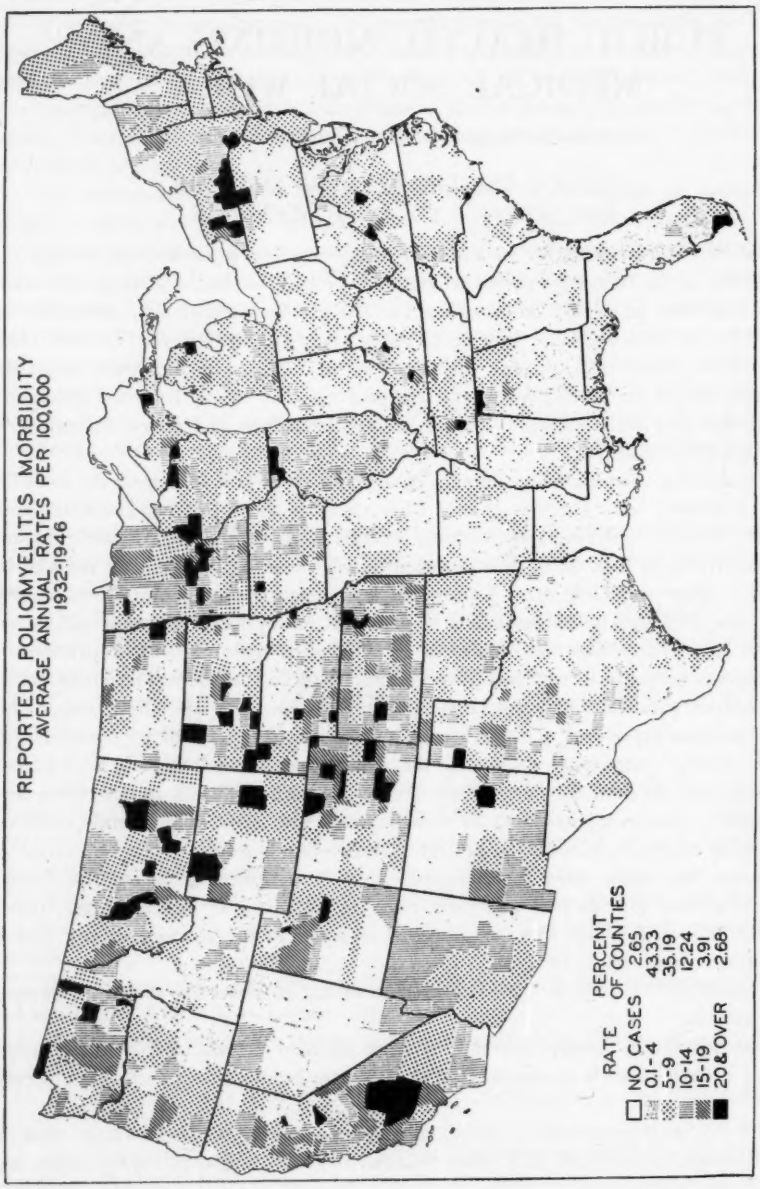

CHART 1. Average annual poliomyelitis morbidity, per 100,000 population, reported in the counties of the United States during the 15-year period, 1932-46, inclusive.

"3. Higher average annual rates appeared to prevail in the northern section.

"Further analysis of these rates confirmed the impression, gained from review of the map, that the rates reported from the northern counties were higher in the period under review. It cannot be determined from these data, however, whether the reported differences between northern and southern sections are due to differences in actual incidence of manifest disease, to differences in reporting, or to other factors, such as variation in age and racial distribution of populations.

"Analysis of counties in several population groups showed that the southern section was slightly deficient in lightly populated and more greatly deficient in heavily populated counties. For the whole United States counties of 50,000 population or more comprised only about 14% of all counties, included about 63% of the population and accounted for over two-thirds of all cases. Among the northern counties little difference was observed between rates for the different population groups. In southern counties, however, while the average rates were about the same among the groups under 50,000 population, a striking rate increase was observed with population increase in the three classes comprising those of 50,000 and over.

"For the country as a whole the units reporting no cases were limited to the lightly populated counties. Among the rate groups examined, the mode appears in the under 5 per 100,000 class for counties under 50,000 population and in the 5-9 class for more populous counties."

To study the question of epidemic recurrence the authors assumed that an epidemic might conceivably occur in each county in each of the 15 years studied, a total of 46,425 epidemic opportunities. Rates were calculated from the cases reported for each of these instances and the rates classified in broad groups. These data were used as a basis for defining epidemic in relation to the "unusualness" of the rate.

"With poliomyelitis it is not satisfactory to consider as epidemic a rate exceeding average incidence since the average rate frequently is composed largely of a few unusual episodes. Thus, in over half of the epidemic opportunities of this experience no cases at all were recorded.

"What may be regarded in a statistical sense as unusual is a matter of opinion; there are degrees of 'unusualness.' It is general practice, however, to consider as uncommon an event occurring not oftener than about 5 times in 100 opportunities."

The data indicated that on this basis a rate of 35 or more per 100,000 could be considered epidemic in northern counties and a rate of 25 or more per 100,000 in southern counties could be so considered.

"It is not intended to imply that this definition satisfies all requirements needed in a general definition of an epidemic of poliomyelitis but it does reflect actual reported experience. It is further not intended to imply that the definitions of an epidemic derived from these data are necessarily of general application in the United States. These standards are based on observed experience and are subject to revision as further experience accumulates.

"Attention has been focused on the increasing tendency since the late 1930's toward the occurrence of epidemics of poliomyelitis in the southern States. If this tendency towards increase, either in actual incidence or in reporting, has been generally greater in the southern than in the northern States then a different epidemic standard in the two sections has already lost any general significance. Therefore, it must be reiterated that the

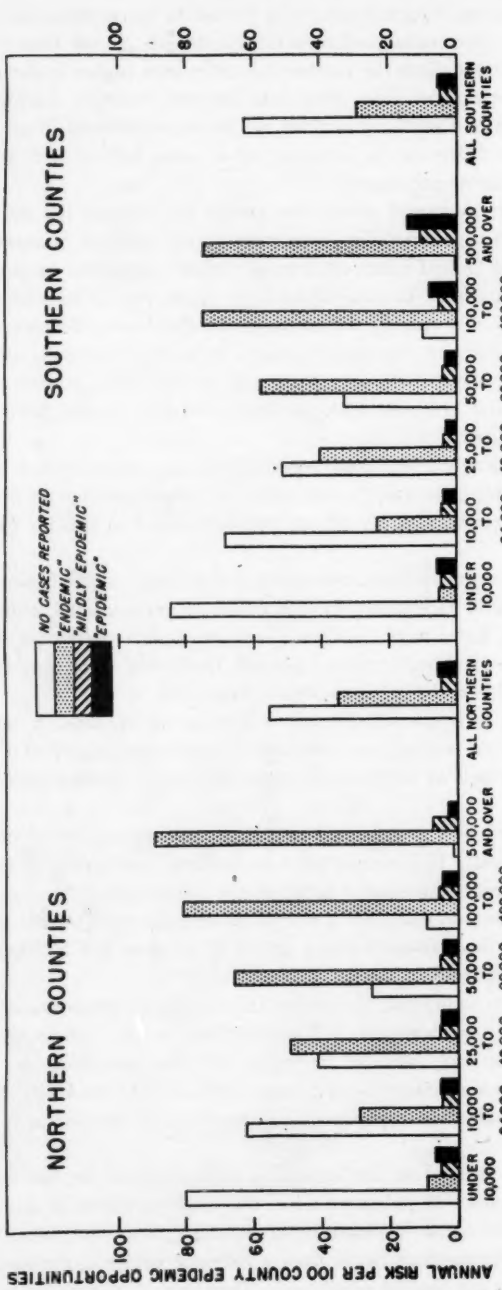

CHART 2. Average annual risk of reported poliomyelitis in northern and southern counties of several population groups during the 15-year period, 1932-46, inclusive.

definitions here presented apply to poliomyelitis reported in the 15 years, 1932 to 1946, and are applicable only to counties and not to reporting units as large as States."

Further division into "degree of epidemicity" was made arbitrarily; rates of 100 or over in both sections of the country were considered as "severely epidemic," rates of 20 to 34 in the north and 15 to 24 in the south as "mildly epidemic" and all lower rates as "endemic."

"Risk related to population of county is illustrated graphically in the chart. [See Chart 2.] Among northern counties epidemic risk is relatively great (0.0646) in counties with less than 10,000 population and decreases regularly as population increases. Thus, though the total risk in 15 years has been shown to be similar for northern counties in all these population classes, the annual risk is inversely related to size of population. Among southern counties annual epidemic risk is similar to northern experience only in counties of less than 100,000. Both annual and total risk increase in the two other population classes."

The average annual probability of an epidemic may be calculated simply by dividing the number of county epidemics observed by the total epidemic opportunities. On the basis of this annual probability it is possible statistically to calculate the chance occurrence of multiple epidemics in the 15 year period. This expectation was compared with the observed recurrence of epidemics in the northern and southern groups of counties over the whole 15 year period, in three 5 year periods and in five 3 year periods.

"The observed frequency of recurrent epidemics within 15 years and within 5 years was not significantly different from that expected on an assumption that recurrence was due to chance. Observed recurrence within 3 years, however, was significantly less frequent."

Tabulation of the interval between epidemics indicated variation from 114 instances of epidemics in successive years to 1 instance of a 13 year interval.

"No particular pattern was apparent in the distribution of yearly intervals between epidemics, though in approximately 50 percent this interval was less than 4 years."

Broad studies such as these serve to bring individual observations into proper perspective. While reports of frequent local recurrences of poliomyelitis or apparent regional differences may seem striking, they appear to be no more than chance variations when viewed in the over-all picture. The epidemiologist, in seeking to explain the way an infection spreads in the community, examines data with the kind of meticulous care apparent in these reports. Clear cut variations in time, place or other factors may offer a clue to the explanation. The failure to find such differences in these data is disappointing.

SPECIAL REVIEWS

JOSEPH STOKES, JR. M.D., *Editor*

WHY SCHOOL HEALTH SERVICE?

By GEORGE M. WHEATLEY, M.D., M.P.H.
New York City

THERE has been a marked change in our concept of the term "school health service." Early activities in this field were almost wholly devoted to the control of communicable disease. Today, thanks to immunization, the antibiotic drugs and health education, most of the old enemies of child health have been conquered. As a result, the years that a child spends in school have been made the healthiest period of life, when appraised by the crude measure of mortality.[1]

Why then school health service? Let me first define what I mean by this term. It comprises health supervision of the school child by educators, public health nurses and school physicians for case-finding and health guidance. At no other time of life is the child or family so readily available for preventive medical service and health education. Public health cannot afford to neglect this ready access to so large a segment of the population—actually more than 20 million persons.

Entrance to kindergarten and first grade is perhaps the most valuable of these opportunities. For all too many children, this is the first health examination since the first year of life. Habit disorders or physical defects which have developed in the preschool years can be brought to light and treatment advised.

A convincing demonstration of the value of a good medical examination at this time of life occurred recently when I was instructing a group of fourth year medical students. As part of their pediatric training, they visited a school to do some examinations under supervision. Their boredom at the prospect of examining a bunch of well children was evident. Each student was assigned a youngster entering school for the first time. They were told to interview the parent and then to make a careful examination. Very soon one of the students returned in much excitement and reported the discovery of a large hydrocele and scrotal hernia. The interview with the mother revealed that the defect had been noticed for some time but she did not believe anything could be done about it.

This is not an isolated situation. For example, Hardy,[2] in a recent study of children entering school, discovered that 75% needed further medical attention, that almost the same percentage had dietary, rest and related problems requiring family health guidance. We know that certain health problems are to be anticipated as children advance in school. For instance, vision, hearing and speech disorders must be looked for and corrected. Fortunately, rapid, validated screening tests can be employed for their detection at systematic intervals during school life. Dental needs are likewise serious and can best be met at this time.

At this time, too, rheumatic heart disease also commonly begins. The school is a strategic place to locate possible cases and to aid in maintaining the continuity of health supervision which these children especially need.

Dr. Wheatley is Third Vice President, Metropolitan Life Insurance Company, New York, N.Y.

Presented at the Section on Preventive Medicine and Industrial Hygiene at the Annual Meeting of the American Medical Association, Atlantic City, N.J., June 10, 1949.

(Received for publication Oct. 20, 1949.)

While healthy emotional patterns and good habits of eating, sleeping and general hygiene should have been established in infancy and the preschool period, nevertheless, much can and should be done during school life to foster these fundamentals for a healthy maturity. This is why it is essential for teachers to be a part of the health service program. Their day to day observation and teaching are vastly more influential in achieving a sound body and a sound mind than the occasional efforts of the physician and nurse.

The physically handicapped child needs particular attention because in some instances further treatment may promise improvement or even cure of the condition. In all cases the school has a special responsibility to appraise the child's potentialities and do all that is reasonable to enable the child to attain his full capacity for work and play.

These are some of the major reasons why school health service is an essential component of the public health program of the community. It is preventive medical service for a fifth of the population.

The strong current of public interest in the health of the school child following World War II is expressed in the National School Health Services Act of 1949 which was recently passed by the Senate without a dissenting vote. This legislation, if enacted, provides 35 million dollars to assist states to improve school services.

This represents a substantial increase in expenditures. States now spend about $24,600,000 for health service in schools; most of this money is spent in cities. There is great variation between cities in the expenditure per pupil.[3] For example, Newark, N.J., spends $5.33, New York City $2.11, Los Angeles $2.74, Pittsburgh $2.94, Chicago $.56, and Detroit $.17. The new legislation leaves the development of the program largely up to the individual states. Are the states prepared to spend this additional money wisely? Medical advice and guidance is needed at the state level and all along the line.

In view of the increasing interest and the prospect of substantial funds to support further work, it is your duty as a physician to concern yourself with this problem. To help you appraise your local service the following questions and comments may be helpful.

1. *Is existing legislation in the state compatible with the development of a medically sound program?*

Approximately three fourths of the states provide for physical examinations or inspections of school children. Many of these laws are obsolete. Some for instance may forbid clothing to be removed, others require a medical examination of every child every year or require that the examination be done by some other individual as, for example, the teacher, principal or school nurse.

With respect to administrative control, some appreciation of the variation which prevails is seen in the following table based on the recent survey of child health services by the American Academy of Pediatrics.[4]

	Agencies giving school medical service	
	No.	Per cent
Official education	1,271	45
Official health	1,173	41
Joint education and health	323	11
Other agencies	84	3
	2,851	100

In general, at the local level, education authorities provide the service in urban localities and health agencies are responsible in rural areas.

2. *Is the relationship between the education and health department conducive to the operation of an effective health service?*

Cooperation between the departments of health and education at the federal, state and local levels is a basic requirement for a good school health service. Fortunately, this is better appreciated today than it was a few years ago. Each department has an important contribution to make to the total program. On the one hand, the health department is the official legally constituted agency with responsibility for the health of the entire community. The health department has the technical personnel and a better perspective of the community's health to enable it to judge best how to spend the taxpayer's health dollars most productively. On the other hand, the education department is legally responsible for the supervision of children in its care throughout the school day. It has the technical personnel and the responsibility for their education. Education departments usually can secure a more adequate budget for school health work than can health departments. Health departments are of more recent origin and other parts of its program compete with school health for tax funds. The money necessary for the school health service represents a smaller item in the total education department budget than in the health department budget. In the latter department, school health service is often the largest single item and when the health department has to reduce expenses, it is likely to cut the school health service budget first because it has the larger portion.

School health authorities are agreed that neither the health department nor education department alone can do the job of providing good school health services.[5] Team work or an active partnership is required because each has a definite role to play. In a number of states we now have interdepartmental committees or councils which bring the two departments together for joint planning and operation. Thus duplication of administrative personnel is avoided and a uniform program can be achieved. This makes for better understanding between the two departments and provides a more intelligent as well as more efficient school health program. Such councils or committees have a place at all levels—national, state and local.

The School Health Services Act, if enacted, would require that state education and health authorities jointly prepare the state plan in order to qualify for federal aid.

3. *Is there an adequate supply of public health nurses serving schools in order to follow-up children with health problems?*

Adequate nursing service must be provided for the follow-up of children with health problems and the other manifold activities of the school nurse. She is the only one who devotes all her time in the school to the care of the child's health. Yet in planning school health services, her key role is sometimes overlooked.

Attention should be given to studying the activities of school nurses to be certain that all her functions are properly those of a public health nurse. Some schools use the nurse as an attendance officer. In other situations she may be doing too much clerical work. Everyone knows that nurses are scarce. Their time must be carefully budgeted for health functions. The Astoria demonstration study found that approximately three hours of nursing time were required for every hour of physician time allocated to a school.[6] Less

nursing time than this built up an overwhelming load of medical problems for follow-up. The most efficient results are usually obtained by the generalized public health nurse who works part-time in the school and part-time in her district. Full-time nurses may be necessary in large schools.

4. *Are health services integrated with health education?*

One of the prime purposes of school health service is to create in the child an understanding and desire for preventive medical service. Unfortunately, this educational objective has rarely been achieved by the usual school medical examination. All too frequently haste and superficiality make it a bad educational experience for the child. We have a responsibility as physicians to help to improve the quality of the school health examination and to make it a truly satisfactory learning experience. While it is not appropriate to make the examination a searching diagnostic procedure, it should be done with as much care as to command medical respect and be of educational value.

With the parent present at the examination, with stress on adequate history taking, with emphasis on interpretation of his findings to parent, nurse and teacher, and careful attention to planning after-care of the child, the school physician can meet his educational opportunities and responsibilities. Under these conditions, he will use facts coming from the teacher and the home which relate to the educational, emotional and social problems of the child.

Several recent contributions on the school health program recognize the importance of defining the functions and education of school health personnel.[7,8]

A committee of a medical society in cooperation with health and education departments might plan a program of refresher courses about child growth and development, common medical problems in children—especially nose and throat conditions, allergy, endocrinology, rheumatic fever and mental hygiene.[9]

5. *Is there competent supervision of the program?*

The professional personnel doing school work need the leadership and guidance which good professional supervision can give. Except for a few urban communities, this type of supervision does not exist at the local level. The supervision which now exists in state health and education departments should be strengthened. Where supervision does not now exist, it could be provided most economically and competently through health departments employing qualified full-time personnel who have training in pediatrics and school health service. This will aid materially to integrate the school health services with the entire child health program of the community.

6. *Does the treatment aspect of the program need strengthening?*

The main objective underlying the school health service is to see that something is done about those children who have health problems. The National School Health Service Act would enable states to provide funds not only for diagnostic service but for treatment. The amount of funds made available will put a practical limitation on this feature. It is logical to urge that the funds be used for vision, hearing and speech disorders which will obviously affect the learning process. State funds should be spent only for the treatment of those children who would otherwise not receive care.

One of the most important ways to strengthen the treatment aspect of school health

service is to develop closer relationships and better understanding between practicing physicians and those administering school health service.

Many physicians fail to realize that the health service is a care-finding and referral agency for them. The practitioner should know that the school health service not only refers patients to him but could perhaps aid him both in diagnosis and follow-up and, in special circumstances, even treatment.

Industry has this same problem. Several industries have taken the initiative to solve it. For example, General Motors has conducted a series of dinner meetings in the cities where they maintain large industrial establishments.[10] Physicians who treat many of the plant workers are invited to hear about the industrial medical department's policies and problems. Visits to the plant are encouraged to see the working operations and to learn some of the working hazards at first hand. These meetings have been very successful in improving the relationship between the plant health service and the community medical facilities.

The follow-up will be strengthened by creating confidence on the part of the practitioner in the school's medical findings.

Many schools are using ineffective, crude methods for the detection of vision and hearing defects. Present technics should be carefully studied in relation to recommended procedures. For example, on vision testing the National Society for the Prevention of Blindness has an excellent guide.[11]

Any procedure to be used for the mass testing of school children for a possible defect should be reviewed and approved by a local medical committee.

The diagnosis and treatment of many of the conditions found in school children, for example, vision and hearing defects, rheumatic fever and heart disease, call for special professional training and experience. In rural areas specialists in these fields often are not available. In some communities children suspected of heart disease or rheumatic fever are referred by school physicians to a children's cardiologist employed by the schools. This service is provided with the approval of the medical society and is similar to diagnostic service provided by health departments for tuberculosis and some other diseases. By this careful procedure, more accurate diagnosis for a serious condition is assured and modification of the school program can be based on a clearer understanding of the child's potentialities. This service should be made available to the practicing physician.

Health supervision is too large a task for the school to do alone. The school should do screening and periodic health examination and health education. The best health education is to teach personal responsibility for health. Children and their parents should learn through the school health service to depend upon the personal physician and dentists not only for treatment, but for supervision of the well child. Many more children would be examined by their own physicians and dentists if schools made this a policy.

Obviously these questions, however important from a medical and administrative point of view, do not raise all the issues involved in the operation of school health service. A comprehensive outline of policies relating to the entire school health program will be found in "Suggested School Health Policies" published by the Committee on School Health Policies of the National Conference for Cooperation in Health Education.[5]

Despite widespread efforts to convince the public of the importance of the periodic health examination, we must face the fact that so far our best efforts have fallen far short of expectations. With the school child we have an unequaled opportunity to create under-

standing of the vital importance of health supervision. If this is made an effective educational experience, the child and other members of the family are likely to understand its importance as a health safeguard throughout life. This is the essence of preventive medicine.

REFERENCES

1. Statistical Bulletin, New York, Metropolitan Life Insurance Company, April 1949.
2. Hardy, Martha C., Study of health needs of Chicago children, Social Service Rev. **19**:201, 1945.
3. Maxwell, Cyrus H., U. S. Office of Education, personal communication to the author. Tentative figures as reported by Superintendents of Schools to the Office of Education.
4. Child Health Services and Pediatric Education, American Academy of Pediatrics, New York, The Commonwealth Fund, 1949, p. 270.
5. Suggested School Health Policies, Health Education Council, New York, 1946.
6. Nyswander, Dorothy B., Solving School Health Problems, New York, Commonwealth Fund, 1942.
7. Educational Qualifications of School Physicians, Am. J. Pub. Health **34**:977, 1944.
8. School Administrator, Physician and Nurse in School Health Program, Monograph 13, New York, Metropolitan Life Insurance Company, 1946.
9. Wheatley, G. M., Physician and school medical services, New England J. Med. **236**:205, 1947.
10. Selby, C., General Motors Corporation, personal communication to the author.
11. Guide for Eye Inspection and Vision Testing, New York, National Society for the Prevention of Blindness, 1949.

One Madison Avenue

NEWS AND ANNOUNCEMENTS

Pediatric Fellowships for General Practitioners

The Division of Graduate Medicine and the Department of Pediatrics at Tulane University of Louisiana School of Medicine, New Orleans, have established plans for continuous training fellowships in pediatrics to meet the needs of general practitioners from rural communities. Applicants should be less than 45 years of age and should have practiced and planned to continue practicing in communities of less than 10,000 population. The course of study will continue for not less than 3 months and will encompass clinical experience in all phases of infant and child health, active participation in the undergraduate and postgraduate teaching programs of the department of pediatrics and opportunity for pursuit of individual clinical or research interests on a part time basis. Appointments will be made on the basis of merit and need. The course will be highly individualized. Application may be made by any qualified person. Responsibility for arranging and paying for registration, tuition and living expenses during the period of fellowship rests with the individual applicant or his sponsoring agency. For information, address the Director of Graduate Medicine, Tulane Medical School, 1430 Tulane Avenue, New Orleans, La.

* * *

The National Foundation for Infantile Paralysis announces that 29 additional research and educational projects in infantile paralysis, totaling $849,738.68 in March of Dimes funds, have been awarded to scientific and technical institutions throughout the United States and Canada.

* * *

The Society for Pediatric Research announces the appointment of the following 7 additional Mead Johnson Fellows for the academic year 1949-1950: Dr. C. T. Lee, China; Dr. Solomon A. Kaplan, South Africa; Dr. Carlos A. Bauza, Uruguay; Dr. Isabelle Valadian, Lebanon; Dr. Ramon Sanz Munoz, Mexico; Dr. Dacio Pinheiro, Brazil; Dr. Jorge Arguedas Soto, Costa Rica.

* * *

The American Board of Pediatrics, Inc., announces that oral examinations will be held at:
Philadelphia—March 31, April 1 and 2, 1950
Cincinnati—May 5, 6, and 7, 1950
San Francisco—June 30, July 1 and 2, 1950
Chicago—October 1950
Boston—November 1950

Complete information concerning further details may be obtained from: The Executive Secretary, 6 Cushman Road, Rosemont, Pa.

The following candidates were certified by the American Board of Pediatrics at Chicago, Ill., Dec. 9, 10 and 11, 1949.

Abramson, Harry, 14 W. Young St., Somerville, N.J.
Blevins, Theodore Pollard, 1400 W. Jefferson Blvd., Los Angeles 7, Calif.
Borne, Stanford, 32 E. Mineola Ave., Valley Stream, L.I., N.Y.
Brewer, Wilson Kenneth, 503 S. 7th St., Springfield, Ill.
Butscher, William Charles, 5919 Greene St., Philadelphia 44, Pa.
Campbell, Winona Gould, 4200 E. 9th Ave., Denver, Colo.
Chastain, Philip J., 103 Douglas Entrance, Coral Gables, Fla.
Colon-Rivera, Egidio S., Torre de La Vega #1300 Ave. Fernandez-Junior Stop 18½, Santurce, P.R.
Finkelstein, Malvin, 2139 Hudson Blvd., Jersey City 5, N.J.
Fleming, Arthur W., 5307 Hyde Park Blvd., Chicago 15, Ill.
Fletcher, Mary Walker Critz, 2905 LaBranch, Houston, Tex.
Flett, James, Jr., Univ. of Colorado Medical Center, 4200 E. 9th Ave., Denver 7, Colo.
Fried, Charles Tear, 1220 Grand Concourse, Bronx 56, N.Y.
Geller, Morton Jerome, 75-04 185th St., Flushing, N.Y.
Haddon, Joseph E., 532 5th St., Bremerton, Wash.

Handelman, Nathan Irwin, 3618 Lexington Rd., Louisville 7, Ky.
Holley, Edward Boyd, 1020 Boston Bldg., Salt Lake City, Utah
Hughes, Wilson Emery, 150 Purchase St., Fall River, Mass.
Iams, Alexander M., 110 E. Main St., Madison, Wis.
Kahn, Alexander Jerome, 3120 N. Meridian St., Indianapolis, Ind.
Kaplan, Martin Z., 840 Barret Ave., Louisville, Ky.
Kirk, Thomas Rogers, Burns Clinic, Petoskey, Mich.
Kutch, Joseph Harry, 251-15 Union Turnpike, Bellerose 6, L.I., N.Y.
Larrabee, John A., 2455 N.W. Marshall St., Portland, Ore.
Latham, Raymond Waldron, 286 Plaza Theater Building, Kansas City, Mo.
Levitin, Milton, 683 E. Broad St., Columbus 15, Ohio
MacColl, William Alexander, 201 Securities Bldg., Seattle 1, Wash.
Martz, John Charles, 325 N. Euclid, St. Louis 8, Mo.
Michael, Morris Irwin, 3520 Cumberland St., N.W., Washington, D.C.
Miller, Roland E., 1625 Kossuth St., LaFayette, Ind.
Mirman, Ben., 924 E. Main St., Alhambra, Calif.
Mizell, Irving David, 4929 W. Irving Park Rd., Chicago, Ill.
Morse, Lawrence Sewall, 68 Bay State Rd., Boston, Mass.
Moyer, Forrest George, 227 N. 17th St., Allentown, Pa.
Orris, Harry William, 244 Ocean St., Lynn, Mass.
Parkhurst, Frederick B., 500 Downing St., Denver, Colo.
Petersilge, Carl L., 13 W. Church St., Newark, Ohio
Rabe, Edward F., University of Kansas School of Medicine, Kansas City, Mo.
Rumble, Charles Taylor, 700 Spring St., Macon, Ga.
Runner, Charles Jefferson, 6 E. Garfield Blvd., Chicago 15, Ill.
Scott, Earl S., 255 S. 17th St., Philadelphia 3, Pa.
Slotkowski, Eugene L., 5815 N. Kolmar Ave., Chicago, Ill.
Statman, Bernhardt J., 849 S. 12th St., Newark, N.J.
Stefano, Umberto, 206 E. 15th St., New York 3, N.Y.
Untracht, Samuel, 50 E. 78th St., New York 21, N.Y.
Walsh, Edward Francis, 868 Lowry Medical Arts Bldg., St. Paul, Minn.

* * *

Sixth International Congress of Pædiatrics, Zurich 1950

Fourth Communication

The provisional programme ("Meeting Information") of the Sixth International Congress of Pædiatrics Zurich 1950 (24th-28th July, and 21st-31st July resp.) has been circulated to the presidents of national pædiatric associations in all countries through the agencies of the American Express Co., Inc. and the foreign Diplomatic Representatives in Berne. The programme is available to anybody who is interested either through the offices of the pædiatric association of his own country or through the American Express Co. A short synopsis of the events that are scheduled to take place at the time of the Congress is given below:

(1) Scientific and Industrial Exhibition in conjunction with an Exhibition organized by the World Health Organization which will be open to the public. Duration: July 21st-31st.

(2) Advanced lectures on many topics in connexion with Pædiatrics will be delivered in different languages during the Exhibition.

(3) There will be conducted tours and demonstrations (in different languages) through a number of hospitals and welfare institutions, etc., of the town of Zurich and the neighboring districts.

(4) Nurses and sisters of many countries will be invited through the International Council of Nurses to attend a Conference from July 28-29th, 1950.

Requests have been sent through the Swiss Diplomatic Service to the governments of 62 countries to send official representatives to the Congress. We would ask the governing bodies of all national Pædiatric Societies to assist in the nomination of these delegates in order that we may have to hand the names of the officially appointed representatives before February 1st, 1950.

The President: Prof. G. Fanconi
The Secretary General: Dr. H. Zellweger

Special Notices

1. *Further Information Concerning the Reading of Papers*

A provisional programme for the group lectures was published in the Second Communication (Helv. Paed. Acta, vol. 4 [1949], fasc. 1, p. 3-14) and in "Meeting Information." It has been decided that in Section XII papers may be read and material may be presented that is of importance but falls outside the province of the subject matter that was originally allowed by the Committee of the Congress. Since it is imperative to complete the programme as soon as possible we would ask all those who intend to make an important contribution to any of the subjects or to section XII, to let the secretary know of their intention and to furnish him with the title of their brief communication without delay. All communications should be addressed to Dr. H. Zellweger, P.-D., Kinderspital, Zürich 32. The last date for receiving communications is the 15th January, 1950.

The time allowed for the communications is 5-10 minutes. Should it happen that too many papers are submitted on any particular subject, then the Committee of the Congress reserve the right to refuse papers in order that sufficient time may be left for the discussion. Every reader of a paper that has been accepted will receive a note to guide him as to (a) the time at his disposal, (b) arrangements for printing the communication, and (c) final date for handing in the manuscript.

2. *Film Demonstrations*

Films (16 mm and 35 mm, silent or sound) may be shown from the 21st-31st, July, 1950, in a room specially reserved for the purpose. The films must be of a scientific or educational subject. Films that are to be shown must have a permit from the Committee; those interested should write to the secretary for special application forms. The following details should be furnished: title, short summary of contents, name of producer and date, length of the film, running time and type (width, silent or sound or colour film). Final date for applications to be received: 15th January, 1950.

3. *Demonstrations of Special Apparatus and Experiments*

Applications should be made as early as possible, so that we can provide sufficient room and facilities. Final date: 15th January, 1950.

4. *Scientific Exhibition*

Every clinician or research scientist is entitled to present his observations as long as such work is of recent origin and does not date back further than 1947. Each exhibit should be the work of the individual presenting it and will be shown under his name. Since each section of the exhibition serves one particular subject, it is important that each contributor confines himself to one item for display. This does not exclude the possibility that a research foundation might not exhibit a variety of objects through its different members. It is, of course, desirable that the exhibitor should be at the disposal of the visitors for certain hours of the day to give information and to answer questions.

Facilities provided: Booths are available to exhibitors that are about 2 metres deep, 2 metres wide and 1½ metres high, that is, about 9 sq. metres exhibition space. No charge is made for these booths. Each booth is provided with light plug connexions and with a small table and chair. Small amounts of tabular material can be exhibited on a special wall that is reserved for such matter. Microscopes are available if notice is received in good time. Illuminated show cases can only be supplied if they are paid for in advance to the Organizing secretary. For exhibition in these cases only lantern slides with a width of 12 cm by a height of 9 cm, or 5 cm by 5 cm are admissible. The voltage is 220 Volt.

All enquiries in connexion with the exhibition should be addressed to Dr. C. Gasser, Kinderspital, Zürich 32. Explicit directions will be sent to all prospective exhibitors. The last date for registering is the 15th February, 1950. Application forms should be accompanied by a short summary of the material for exhibition. The Committee of Management reserve the right to make a selection of the material submitted if there is more than the exhibition has room for.

5. *Publication of Communications*

See under "Special Notices" Helv. Paed. Acta, vol. 4 (1949), fasc. 2, p. 105, item 6.

6. Registration of Visitors to the Congress

Participants must register with the Agencies of the American Express Co., Inc. or their correspondents before the 1st January, 1950, since the company have been appointed our official agents. The matter has been referred to previously in "Meeting Information." Visitors from Bulgaria, Jugoslavia, Poland, Rumania, and Russia should register directly with the Committee of the Congress in Zurich. Registration should be affected as soon as possible since there will be some difficulty in finding accommodation in Zurich for all visitors to the Congress. Those coming from over-sea should also keep in mind that 1950 is a "Holy Year" and that all transport will be heavily booked, hence early registration is essential.

In "Meeting Information" we gave a list of lodgings and, in addition, a restricted number of lodgings have now been secured in private families. The latter are reserved in the first instance for lecturers and exhibitors and for colleagues who have to travel under restricted financial circumstances. Clinical Assistants who wish to avail themselves of this offer should communicate directly with the general secretary of the Organizing Committee. The applicant should enclose a recommendation from the Director of his Clinic or from the President of his national Pædiatric Association.

Swiss Air Lines and TWA have agreed to grant the usual 10% reduction on return tickets and in addition they have a sliding scale arrangement of reductions for groups of 5, 10 or more people travelling together. Information as regards the purchase of such tickets as well as any information relating to price reductions for sea passages and travelling on other air lines should be directed to the American Express Co., Inc.

ADDENDUM

In order to avoid misunderstandings, we should like to draw your attention to the fact that the amount of Swiss Francs 250.- to Swiss Francs 433.- for board and lodging in hotels mentioned in the "Meeting Information" does include the charge for the congress card of Swiss Francs 100.-. On the other hand, the amount of Swiss Francs 100.- for the congress card is not included in the charge for board and lodging in dormitories and private rooms of students which is Swiss Francs 10.- per day.

* * *

Dr. Lawson Wilkins delivered the 18th annual series of the Benjamin Knox Rachford Lectureships on Feb. 7 and 8, 1950, at 8:30 p.m. in the auditorium of the Children's Hospital Clinic and Research Building, Cincinnati, Ohio. His lectures dealt with the role of hormones in regulating somatic and sexual development.

* * *

Dr. John A. Toomey died on Jan. 1, 1950, at his home in Cleveland. He was taken ill with a heart attack while attending the Second Pan American Congress of Pediatrics in Mexico City. Dr. Toomey was a Fellow of the Academy and a past President. He was head of City Hospital's contagious-disease division for 27 years and was a professor at Western Reserve University Medical School.

* * *

Dr. Stanley Hetfield Nichols, Asbury Park, N.J., died on Nov. 14, 1949. He was a Fellow of the American Academy of Pediatrics.

BOOK REVIEWS

FETAL AND NEONATAL DEATH, revised edition, Edith L. Potter, M.D., and Fred L. Adair, M.D., Chicago, The University of Chicago Press, 1949, $3.75, 173 pp.

This book attempts to tell the person interested in fetal and neonatal mortality what to look for and how, in a relatively unknown field in medicine. Obviously in an area in which so little fundamental research has been done it is, as the authors state, a matter of personal opinion whether one can state the cause of death in any infant. With this humble point of view and with the basic information available in this book, the opportunity exists for making a rational approach to the problem. The book contains many helpful tables and photographs illustrating important points. It should be available to all who are interested in fetal and neonatal mortality.

TRENDS IN MEDICAL EDUCATION, The New York Academy of Medicine Institute on Medical Education, edited by Mahlon Ashford, M.D., New York, The Commonwealth Fund, 1949, $3.00, 320 pp.

The origin and scope of this book is succinctly described in the following excerpts from the foreword by the Editor:

"The Committee on Medical Education of the New York Academy of Medicine . . . conducted an Institute on Medical Education in 1947.

"Six conferences were held, each of which is recorded in a chapter of this book. These conferences were conducted as round table or panel discussions. Nationally distinguished experts were chosen to present appropriate topics and to exchange views, after which general discussion took place.

"The Committee on Medical Education offers the proceedings of this Institute as a practical presentation of current problems and trends in medical education in the United States at this time."

The subjects of the six conferences were: Premedical Education and the Selection of Medical Students; Undergraduate Medical Education; The Medical Education of Interns and Residents; Graduate and Postgraduate Training for Specialization; The Responsibility of Medical Schools and Hospitals in the Education of the General Practitioner; The Relation of Group Practice and Community Medical Services to Medical Education.

It is inevitable that in a book which represents 38 different papers, there should be great disparity in quality of content as well as in literary style. Further, it is the rare "discusser" indeed who, even after editing, can see his remarks in print and be pleased with the result. Although some of the 60-odd discussions and opening or closing remarks represent prepared papers, most of them are "off the cuff." The above factors do not enhance the readability of the book as a unit.

Many of the papers show thoughtful preparation and are valuable contributions to their segment of the problem. Every chapter contains interesting and provocative ideas, and medical educators concerned with broad problems will benefit by a general perusal of the volume. Anyone interested in a specific subject covered by one of the chapters should assuredly read that chapter.

As a whole the book represents a valuable commentary on contemporary thinking in medical education.

TECHNIK DER KINDERAERZTLICHEN DIFFERENTIAL DIAGNOSTIK, Prof. Dr. Alphons Solé, Benno Schwabe & Company, Basel, Switzerland, 1948, Swiss francs 20, 384 pp.

This book on differential diagnosis is devoted to the general practitioner. The skeleton of the book is made up of 21 charts in which the corresponding syndromes are systematically outlined and in many instances the logical differentiation can be drawn from them. The emphasis is always placed on the most common diseases. The most frequent errors of the general practitioner are revealed with painstaking care.

The case history, which in pediatric practice is usually obtained from one or more excited relatives, is frequently undependable and great care must be used in evaluating it. Of prime importance is the clinical impression which should at once give a clear intuitive picture to the experienced

glance of the doctor. This clear sightedness has always played a great role in the Viennese school and is called "der aerztliche Blick."

Another typical Viennese feature is found in the chapter dealing with 19 different facial expressions. It is true that many doctors put too much emphasis on laboratory reports and neglect what is lying often before their eyes. However, a diagnosis by the impression of a "facies helminthica" or "facies malarica" should not be pronounced if it is based only on the doctor's glance at the child's face. The portrait of hysteric manifestations seems somewhat too primitive even for the general practitioner.

In conclusion pediatric data are listed which are essential to every physician and the tables are repeated for a quick review. The second print of the charts would have been of greater value if the differential diagnosis had been carried out somewhat further and had included diseases that are not so commonly encountered or even not so commonly diagnosed as many physicians are not familiar with them. The differential diagnosis of hemolysis, of Guillain Barré's syndrome, cystic fibrosis of the pancreas, toxoplasmosis are important also to the European physician. Also gall stones and diseases of the bile duct should not be excluded. In the last instance the doctor's glance can only recognize what he knows.

The style and format of the book are excellent. It fulfills definitely its purpose and will prove a valuable aid to any physician.

EINFUEHRUNG IN DIE KINDERHEILKUNDE, 195 Lectures for Students and Physicians, ed. 3, E. Glanzmann, M.D., Vienna, Springer-Verlag OHG, 1949, 14.40 *s*, 986 pp. with illustrations.

This is an outstanding textbook and it is clear that the author is an excellent clinician and teacher. The book is already in its third edition. Originally published in two volumes, it is now concentrated into one volume. The book consists of 195 lectures, which in many instances contain a case history. There are 287 excellent illustrations; the book is comprehensive, and deals with pediatric problems in a clear manner. The first lectures are devoted to nutrition, growth and development, and alimentary disorders. This is followed by an extensive discussion of blood diseases (140 pages being devoted to this subject); Glanzmann has always been exceedingly interested in hematologic problems (e.g., anaphylactic purpura). The book further contains an able presentation of hereditary and congenital conditions, infectious diseases and tuberculosis. Moreover psychologic problems are not overlooked. The final lecture deals with ophthalmologic conditions. Erythroblastosis and the role of the Rh factor are completely reported. Of interest is the report of cases of erythroblastosis showing cystic fibrosis of the pancreas and celiac features. Electrolytes in gastrointestinal disorders are fully discussed, and also the vitamins. Darrow's studies are reported. The author quotes the detoxifying effect of vitamin C upon the toxin of the Bac. Bordet-Gengou and recommends the use of 500 mg. vitamin C against pertussis.

In treatment of diarrheas he advocates the administration of the "Carrotsoup of Moro," which now can be prepared from powdered carrots and Arobon (Nestle), called in the United States Carobflour (St. John's Bread). The effect is similar to that of the apple diet.

In the lecture on multiple aberrations, 10 pages are devoted to a disease called *Bonnevie-Ullrich syndrome,* a condition not found in our literature. The explanation of the symptoms is derived from the results of the experimental studies of Bagg and Little who produced eye abnormalities and foot deformities in mice embryos by exposure to roentgen rays. Intensive hypersecretion of liquor fluid sets in and the accumulation of excessive fluid leads to a break through the surrounding membrane. In human beings several anomalies can be traced to such an abnormal accumulation of excessive liquor. Some of the characteristic features are hypertelorism, cutis laxa of the neck and at the buttocks, hypoplasia of the mandibula, and low seated earlobes. The effect of rubella on the embryo is briefly mentioned in the ophthalmologic section.

THE CHEST AND THE HEART, vols. 1 and 2, edited by J. Arthur Myers, Ph.D., M.D., and C. A. McKinley, M.D., Springfield, Ill., Charles C Thomas, Publisher, 1948, 1800 pp., $25.50.

Although the main interest in these splendidly edited volumes is directed to problems of internal medicine, the pediatrician will find much of value in them. About 60 different authors are con-

tributors. Volume I has about 1000 pages. The subject matter, however, is not strictly according to the volumes but is divided into Sections I and II dealing with the chest and heart, respectively. Section I contains 64 chapters and comprises about 70% of the material, all of Volume I and part of Volume II. Section I has been edited by J. Arthur Myers. The first chapter, written by Richard E. Scammon, deals with the developmental anatomy of the chest and the thoracic organs; hence, the student of pediatrics should find this of interest particularly in view of the current emphasis placed on the subject of growth and development. Chapter 3, which is a discussion of the physiology of respiration by Maurice B. Visscher and Victor Lorber, is also recommended. Another chapter of an introductory nature is on the subject of the examination of the normal chest in infancy and childhood by the late Chester A. Stewart. Other chapters dealing with miscellaneous diseases that are encountered in the childhood period are on the following subjects: pertussis, by William L. Bradford; the common cold, by Harold S. Diehl; pneumonia, by C. A. McKinley; cystic diseases of the lungs, by L. J. Moorman; pulmonary mycoses, by D. T. Smith. Over 500 pages are devoted to the subject of tuberculosis. Of special interest to the pediatrician is chapter 43 entitled the "First Infection Type of Tuberculosis" by Dr. Myers. Appropriately enough, in view of the current revival of interest in immunization procedures against this disease, BCG is discussed in some detail. Myers takes the view that no dependable immunity is produced by the first infection type of tuberculosis and he is not enthusiastic about the results of immunization with any known agents. Quite naturally, the greater part of the material presented deals with tuberculosis as it appears in the adult subject. There are chapters on various types of treatment: pneumothorax, extrapleural pneumothorax, thoracoplasty, artificial pneumoperitoneum and intrapleural pneumolysis. Although the title of the book is *The Chest and the Heart,* there are chapters on such subjects as tuberculosis of the abdomen, urogenital tuberculosis and tuberculosis of the bone and joint. In addition, there are 3 chapters dealing with the public health aspects of the problem of tuberculosis which are invaluable to all interested in the broader aspects of this disease and its control. Much valuable information to the student of tuberculosis can be found in this collection of writings by the various specialists. It should be pointed out that J. Arthur Myers, the author of several of the chapters on tuberculosis and a recognized authority in this field, differs with some of the current concepts in regard to the disease. Those of us who have been particularly interested in childhood tuberculosis believe his ideas are essentially sound. Section II contains 22 chapters in which the main emphasis is on diseases of the heart in the adult subject. S. Marx White discusses the examination of the heart. Chapters on roentgenologic examination and electrocardiogram are valuable. The subject of congenital heart disease is not given the prominence compatible with its present day importance. This is especially true for the surgical aspects of the problem. Functional cardiovascular disturbances are considered well by George R. Herrmann and the pediatrician will find the subject of cardiac arrhythmia handily presented. The problem of rheumatic fever and rheumatic heart disease is dealt with from the pediatric viewpoint in a rather extensive discussion. Of course, the subjects of pericarditis and endocarditis are always of concern to the child specialist; however, hypertension, coronary sclerosis and the treatment of heart failure, although dealt with well, do not have as much appeal to the pediatrician. Special features to be commended are the summaries and bibliographies at the ends of chapters and the excellent photographic reproductions. These volumes are recommended as valuable general references to the general physician and likewise will be distinctly useful to the specialist in children's diseases.